Cochrane Library

Cochrane Database of Systematic Reviews

Screening for type 2 diabetes mellitus (Review)

Peer N, Balakrishna Y, Durao S

Peer N, Balakrishna Y, Durao S.
Screening for type 2 diabetes mellitus.
Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD005266.
DOI: 10.1002/14651858.CD005266.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Screening for type 2 diabetes mellitus

Nasheeta Peer[1], Yusentha Balakrishna[2], Solange Durao[3]

[1]Non-communicable Diseases Research Unit, South African Medical Research Council, Durban, South Africa. [2]Biostatistics Unit, South African Medical Research Council, Durban, South Africa. [3]Cochrane South Africa, South African Medical Research Council, Cape Town, South Africa

Contact: Solange Durao, solange.durao@mrc.ac.za.

Editorial group: Cochrane Metabolic and Endocrine Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 6, 2020.

Citation: Peer N, Balakrishna Y, Durao S. Screening for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No.: CD005266. DOI: 10.1002/14651858.CD005266.pub2.

ABSTRACT

Background

Diabetes mellitus, a metabolic disorder characterised by hyperglycaemia and associated with a heavy burden of microvascular and macrovascular complications, frequently remains undiagnosed. Screening of apparently healthy individuals may lead to early detection and treatment of type 2 diabetes mellitus and may prevent or delay the development of related complications.

Objectives

To assess the effects of screening for type 2 diabetes mellitus.

Search methods

We searched CENTRAL, MEDLINE, LILACS, the WHO ICTRP, and ClinicalTrials.gov from inception. The date of the last search was May 2019 for all databases. We applied no language restrictions.

Selection criteria

We included randomised controlled trials involving adults and children without known diabetes mellitus, conducted over at least three months, that assessed the effect of diabetes screening (mass, targeted, or opportunistic) compared to no diabetes screening.

Data collection and analysis

Two review authors independently screened titles and abstracts for potential relevance and reviewed the full-texts of potentially relevant studies, extracted data, and carried out 'Risk of bias' assessment using the Cochrane 'Risk of bias' tool. We assessed the overall certainty of the evidence using the GRADE approach.

Main results

We screened 4651 titles and abstracts identified by the search and assessed 92 full-texts/records for inclusion. We included one cluster-randomised trial, the ADDITION-Cambridge study, which involved 20,184 participants from 33 general practices in Eastern England and assessed the effects of inviting versus not inviting high-risk individuals to screening for diabetes. The diabetes risk score was used to identify high-risk individuals; it comprised variables relating to age, sex, body mass index, and the use of prescribed steroid and anti-hypertensive medication. Twenty-seven practices were randomised to the screening group (11,737 participants actually attending screening) and 5 practices to the no-screening group (4137 participants). In both groups, 36% of participants were women; the average age of participants was 58.2 years in the screening group and 57.9 years in the no-screening group. Almost half of participants in both groups were on antihypertensive medication. The findings from the first phase of this study indicate that screening compared to no screening for type 2 diabetes did not show a clear difference in all-cause mortality (hazard ratio (HR) 1.06, 95% confidence interval (CI) 0.90 to 1.25, low-certainty evidence). Screening compared to no screening for type 2 diabetes mellitus showed an HR of 1.26, 95% CI 0.75 to 2.12 (low-certainty

evidence) for diabetes-related mortality (based on whether diabetes was reported as a cause of death on the death certificate). Diabetes-related morbidity and health-related quality of life were only reported in a subsample and did not show a substantial difference between the screening intervention and control. The included study did not report on adverse events, incidence of type 2 diabetes, glycosylated haemoglobin A1c (HbA1c), and socioeconomic effects.

Authors' conclusions

We are uncertain about the effects of screening for type 2 diabetes on all-cause mortality and diabetes-related mortality. Evidence was available from one study only. We are therefore unable to draw any firm conclusions relating to the health outcomes of early type 2 diabetes mellitus screening. Furthermore, the included study did not assess all of the outcomes prespecified in the review (diabetes-related morbidity, incidence of type 2 diabetes, health-related quality of life, adverse events, socioeconomic effects).

PLAIN LANGUAGE SUMMARY

Screening for type 2 diabetes mellitus

Review question

What are the health effects of screening compared to not screening for type 2 diabetes mellitus?

Background

Type 2 diabetes mellitus is a metabolic disorder characterised by high blood sugar which can lead to complications like kidney and eye disease. It can develop at any age but usually peaks in adults 65 years of age and above and may be treated in the beginning through diet and exercise. Type 2 diabetes mellitus may have no or few symptoms at the start and thus may go undiagnosed. Screening of apparently healthy people could lead to early detection and treatment of type 2 diabetes mellitus as well as prevent or delay the development of related complications.

Study characteristics

We found one randomised controlled trial (a clinical study in which participants are assigned to one of two or more treatment groups using a random method) where 20,184 high-risk individuals from 33 general practices in Eastern England were either invited or not invited to screening for type 2 diabetes (the ADDITION-Cambridge study). Eligible participants had to have an elevated diabetes risk score but no known diabetes. The diabetes risk score to identify high-risk individuals comprised variables relating to age, sex, body mass index, and the use of prescribed steroids and anti-hypertensive medication. Practices were eligible to participate if they could provide data for calculation of the risk score for at least 70% of their patients. A total of 11,737 participants attended screening in actuality, and 4137 participants represented the no-screening group. In both groups, 36% of participants were women; the average age of participants was 58.2 years in the screening group and 57.9 years in the no-screening group. Almost half of participants in both groups were on medication for high blood pressure.

This evidence is up-to-date as of May 2019.

Key results

We are uncertain about the effects on screening for type 2 diabetes mellitus on death from any cause and death from diabetes-related causes (the only outcomes of importance for our review for which study authors provided reliable data). The included study did not report on side effects of screening, new cases of type 2 diabetes, health-related quality of life, glycosylated haemoglobin A1c (HbA1c) as a long-term measurement of glucose control, and socioeconomic effects (such as costs of screening, use of medication, number of consultations).

Certainty of the evidence

We based the certainty of the evidence on only one study. The overall certainty of the results from this study is low, because the results are not precise, that is they could change in any direction if new studies are published.

SUMMARY OF FINDINGS

Summary of findings 1. Screening for type 2 diabetes mellitus

Screening for type 2 diabetes mellitus

Population: individuals without known diabetes mellitus but at high risk for the condition

Settings: primary healthcare clinics in Eastern England

Intervention: invitation to screening followed by intensive treatment or routine care of participants with screen-detected diabetes

Comparison: no invitation to screening for type 2 diabetes mellitus

Outcomes	No screening	Screening	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Median follow-up: 9.6 years	**91 per 1000**	**96 per 1000** (82 to 113)	**HR 1.06** (0.90 to 1.25)	20,184 (1)	⊕⊕⊖⊖ **low** [a]	
Diabetes-related mortality Assessed according to whether diabetes was included anywhere on the death certificate Follow-up: 10 years	**4 per 1000**	**5 per 1000** (3 to 8)	**HR 1.26** (0.75 to 2.12)	20,184 (1)	⊕⊕⊖⊖ **low** [b]	
Diabetes-related morbidity	See comment					No substantial difference on self-reported cardiovascular events in a subsample (15% of participants in the screening group and 40% of participants in the control group)
Incidence of type 2 diabetes	**Not reported**					
Health-related quality of life	See comment					No substantial difference on self-reported health-related quality of life in a subsample (the response rate was 62% in the screening group and 53% in the control group)
Adverse events	**Not reported**					

Socioeconomic effects	**Not reported**

CI: confidence interval; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by two levels due to serious imprecision (CI includes both benefit and harm; one study only).
[b]Downgraded by two levels due to serious imprecision (CI includes both benefit and harm; one study only; not a common event).

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. It is characterised by chronic hyperglycaemia and is associated with a heavy health burden of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular, peripheral vascular, and cerebrovascular disease) (WHO 1999). Notwithstanding, approximately one-third to one-half of all people with type 2 diabetes mellitus (now referred to as diabetes), the most common form of the disease, remain undiagnosed (IDF 2019). This is due to the long pre-clinical period (Harris 1992), as well as inadequate access to care, particularly in low- and middle-income country settings (Peer 2014). Early detection and treatment of diabetes may prevent or delay the development of related complications, as demonstrated in the United Kingdom Prospective Diabetes Study (Colagiuri 2002).

Description of the intervention

Screening programmes

Screening is defined as the possible identification of unrecognised disease amongst apparently healthy individuals by means of tests or examinations conducted to identify those at an increased risk for the condition (Standing committee on screening 2018). The aim is to reduce the burden of the disease in the population including disease incidence, morbidity, or mortality. This is achieved through early intervention to reduce the individual risk of the disease, for example a hysterectomy in the pre-cancerous phase to prevent cervical cancer or to improve disease outcomes (i.e. early detection of cancers in general to prevent their spread). Screening is therefore only relevant if detecting the disease early has a significant impact on outcomes and if it leads to marked reductions in advanced disease (Carroll 2015).

Screening programmes may be implemented in different ways, for example population-wide screening for all individuals irrespective of their age or gender, targeted screening for those known to be at higher risk for certain conditions, or opportunistic screening at the point-of-care for other conditions (Durão 2015). The choice of, as well as the need for, a screening programme will depend on various factors. These include aspects related to: 1) disease (severity, prevalence, possible detection in the pre-clinical phase, long latency period, improved outcomes with early detection), 2) screening test (validity, reliability, ease of use, ability for pre-clinical detection of disease), and 3) screening programme (ADA 2002; Grimes 2002).

Key criteria for a screening programme are that it should respond to a recognised need, have clear objectives, and target a defined population (Andermann 2008). Importantly, there must be scientific evidence that demonstrates the effectiveness of the screening programme. Furthermore, case-finding, including diagnosis and treatment, should be economically cost-effective.

Screening for diabetes

Diabetes has a long pre-clinical phase during which raised blood glucose levels contribute to the development of complications. It is therefore a disease that may be suitable for early detection through a screening programme, and many clinical guidelines now recommend early identification of diabetes through screening for the condition (ADA 2003; Borch-Johnsen 2003; Canadian Task Force 2012; IDF 2012). The aim is to identify asymptomatic individuals with diabetes so as to implement therapy early and thus impact favourably on the disease course (Grimes 2002).

Universal, that is population-wide, screening for undiagnosed diabetes is not recommended because it may be poorly targeted and fail to reach the groups most at risk. Individuals at low risk and even those already diagnosed with diabetes may be inappropriately tested (ADA 2002). Screening should be undertaken in high-risk individuals to increase the likelihood of diabetes detection as well as to increase the cost-effectiveness of testing (ADA 2003). In fact, the International Diabetes Federation (IDF) recommends that diabetes screening programmes be opportunistic and limited to high-risk individuals in specific settings (IDF 2012). High-risk individuals may be identified on screening questions with an increased risk for diabetes associated with older age, a family history of diabetes, or the presence of cardiovascular risk factors such as obesity and hypertension, amongst other variables.

The tests that may be used for diabetes screening are the same as those used to make a diagnosis. These include the oral glucose tolerance test, which is perhaps the optimal, but also the most cumbersome, of the test instruments. It is time consuming, requiring two hours for completion, and involves pre-planning for an overnight fast, and is thus not an ideal screening tool. Other tests used to screen or diagnose diabetes include fasting or random (casual) glucose levels (IDF 2012; WHO 1999). Glycated haemoglobin A1c (HbA1c) levels is an additional test that has been recently used (IDF 2012). Screening tools to identify individuals at high risk for diabetes usually entail point-of-care tests using capillary blood.

Adverse effects of screening

Screening for a medical condition can have psychological, physical, and financial adverse consequences. This is particularly relevant with a false-positive result, where overdiagnosis, and subsequent overtreatment, may have detrimental consequences (Carroll 2015). However, the literature on the adverse effects associated with screen-detected diabetes is limited (Selph 2015). Whilst two randomised controlled trials (RCTs) found diabetes screening to be associated with higher levels of short-term anxiety and worry, the overall impact was minimal with no clear long-term negative effects on psychological outcomes (Selph 2015; Sherifali 2013).

How the intervention might work

Screening asymptomatic individuals for diabetes may identify the disease earlier (Selph 2015). The duration of the hyperglycaemic period prior to diagnosis and treatment is expected to be shortened in screen-detected compared with routinely detected diabetes, which may contribute to fewer macro- and microvascular complications. Also, earlier diagnosis of diabetes may lead to earlier or more intensive management as well as timely management of complications as they develop. The US Preventive Services Task Force recommended diabetes screening in asymptomatic adults with raised blood pressures because more intensive blood pressure control in those with diabetes and hypertension has been associated with a reduced risk for

cardiovascular events, including cardiovascular mortality (Selph 2015).

However, a recent systematic review of meta-analyses and randomised trials demonstrated little reductions in disease-specific and all-cause mortality for diseases with available screening tests and where death is a common outcome (Saquib 2015). Nevertheless, a comparison of the outcomes in people with screen-detected versus routinely detected diabetes who undergo similar management may provide evidence to support or dispute the above rationale.

Why it is important to do this review

Sherifali 2013 reported that modelling studies have shown that population-based screening for high-risk individuals with age and hypertension as risk factors may increase the quality-adjusted life years, and that screening was cost-effective if conducted from the age of 45 years and repeated every three to five years thereafter. A review of previous economic models concluded that screening for diabetes appeared to be cost-effective for those aged 40 to 70 years, especially in the hypertensive and obese subgroups (Waugh 2007). However, a limitation of this study was that instead of using empirical data, it required assumptions relating to glucose control and treatment effectiveness in screened individuals.

Despite the benefits of improved glucose, blood pressure, and lipid control in individuals with diabetes, the benefits on outcomes of early diabetes detection through screening remain unclear (IDF 2012). There is insufficient evidence on the direct benefits of routine screening in the general population (ADA 2008; Diabetes UK 2020; Rutten 2006; WHO 2003). Recently, the efficacy of screening for diabetes followed by intensive treatment or routine care versus no screening (control group) was assessed in the ADDITION study (The Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care). Notably, the United Kingdom arm of the study reported no effect of this approach on 10-year mortality (all-cause, cardiovascular, cancer or other causes) (Simmons 2012). An absence of a significant reduction in 10-year mortality with screening compared to no screening for diabetes was also found in the Ely cohort (Simmons 2011). The systematic review on diabetes screening by the US Preventive Services Task Force in 2015 reported that only Simmons 2012 and Simmons 2011 had evaluated the effects of diabetes screening versus no screening on mortality (Selph 2015). More evidence is thus required to ascertain the health impact of diabetes screening.

Furthermore, a recent overview of systematic reviews that examined diabetes and hypertension screening programmes identified the need for a systematic review to assess the effectiveness and impact of such screening strategies (Durão 2015). This review aimed to address this gap in the literature, as a review of the current evidence should help determine which of these recommendations is evidence-based and worth following (Inzucchi 2012). This will provide useful guidance for professional associations who despite the unclear link to the evidence base, have issued recommendations about screening for diabetes (ADA 2004; IDF 2012).

OBJECTIVES

To assess the effects of screening for type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs.

Types of participants

Participants were adults and children without known diabetes mellitus.

Diagnostic criteria for type 2 diabetes mellitus

The World Health Organization (WHO) criteria for the diagnosis of diabetes requires the administration of an oral glucose tolerance test (OGTT) (WHO 1999). The test is performed after an overnight fast of 8 to 14 hours. Initially, a fasting blood specimen is drawn followed by the administration of a glucose load. This consists of 75 g anhydrous glucose dissolved in about 250 mL of water. Two hours later a blood specimen is drawn to determine the 2-hour plasma glucose level.

Using this method, the WHO cut-off values for the diagnosis of diabetes in 1985 were ≥ 7.8 mmol/L for fasting plasma glucose and ≥ 11.1 mmol/L for the 2-hour plasma glucose (WHO 1985) (Appendix 1). In 1997, the American Diabetes Association (ADA) proposed that a diagnosis of diabetes be based only on fasting plasma glucose, using a lower threshold of 7.0 mmol/L (Expert Committee 1997).

In 1998, the WHO accepted the ADA proposal to lower the fasting blood glucose threshold to 7.0 mmol/L but retained the use of the OGTT for the diagnosis of diabetes (WHO 1999). In 2003, the ADA aligned their diagnostic criteria for diabetes with that of the WHO (ADA 2003).

Both organisations include a diagnosis of diabetes based on random plasma glucose ≥ 11.1 mmol/L providing that the individual is symptomatic (ADA 2003; WHO 1999). A random blood sample is defined as one that is drawn without reference to the time since the last meal. The typical symptoms of hyperglycaemia include polyuria, polydipsia, nocturia, and unexplained weight loss.

Recently, HbA1c has been recommended as an alternative test to diagnose diabetes. HbA1c is a marker of chronic glycaemia and reflects the average blood glucose level over the previous two to three months. It is usually used in diabetes management to determine glucose control, but advances in instrumentation and standardisation have led to marked improvements in the accuracy and precision of HbA1c assays and its use as a diagnostic tool (ADA 2014; International Expert Committee 2009).

Studies that use the following biochemical screening tests, individually or in combination, to determine diabetes were eligible for this review: capillary, plasma or venous whole blood samples for glucose (random, fasting or after a glucose load) or HbA1c, or urine glucose. This includes studies that used stepwise screening procedures, for example risk assessment questionnaires or database selection, followed by a biochemical test.

Types of interventions

We investigated the following comparison of intervention versus control/comparator.

Intervention

- Diabetes screening (mass, targeted, or opportunistic).

Comparator

- No diabetes screening.

Concomitant interventions had to be the same in both the intervention and comparator groups to establish a fair comparison. For studies with multiple arms, we would include any arm that met the review inclusion criteria.

Minimum follow-up of intervention

Studies with a minimum follow-up of three months were eligible for inclusion.

Summary of specific exclusion criteria

- Gestational diabetes.
- Diabetes insipidus.

Types of outcome measures

We did not exclude any studies on the basis that one or several of our primary or secondary outcome measures were not reported in the publication.

We investigated the following outcomes using the methods and time points specified below.

Primary outcomes

- All-cause mortality
- Diabetes-related mortality
- Diabetes-related morbidity

Secondary outcomes

- Incidence of type 2 diabetes
- HbA1c
- Adverse events
- Health-related quality of life
- Socioeconomic effects

Method of outcome measurement

- All-cause mortality: defined as death due to any cause.
- Diabetes-related mortality: defined as death from ischaemic heart disease (IHD) or stroke.
- Diabetes-related morbidity: defined as development of IHD, stroke, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy.
- Incidence of type 2 diabetes: defined as newly diagnosed diabetes.
- HbA1c: measured in % or mmol/mol.
- Health-related quality of life: evaluated by a validated instrument such as the Diabetes Quality of Life (DQOL) questionnaire.
- Adverse events: e.g. psychological effects such as anxiety, effects of false-positive test results, effects of labelling.
- Socioeconomic effects: defined as healthcare consumption (e.g. use of medication, number of consultations), cost of screening per newly detected individual.

Timing of outcome measurement

- All-cause mortality, diabetes-related mortality, diabetes-related morbidity, incidence of type 2 diabetes mellitus: measured at any time after randomisation.
- HbA1c: measured at any time after randomisation for a diagnosis of diabetes or at least three months postbaseline evaluation for glycaemic control.
- Health-related quality of life, adverse events: measured postbaseline.
- Socioeconomic effects: measured at completion of the study.

Specification of key prognostic variables (with associated magnitude of an important difference)

- Age
- Gender
- Ethnicity
- Family history of diabetes
- Obesity
- Presence of other cardio-metabolic conditions, e.g. hypertension, dyslipidaemia

Search methods for identification of studies

Electronic searches

We searched the following sources from inception of each database to the specified date, with no restrictions on language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (CRSO) (searched 23 May 2019).
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (1946 to 17 April 2019) (searched 23 May 2019).
- LILACS (searched 23 May 2019).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) (searched 23 May 2019).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/) (searched 23 May 2019).

We continuously applied an email alert service for MEDLINE via OvidSP to identify newly published studies using the search strategy detailed in Appendix 1. After we submitted the final update review draft for editorial approval, the Cochrane Metabolic and Endocrine Disorders (CMED) Group performed a complete search update on all databases available at the editorial office and sent the results to the review authors.

Searching other resources

We attempted to identify other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, meta-analyses, and health technology assessment reports. We also contacted authors of the included studies to identify any additional information on the retrieved studies and to determine if further studies existed that we may have missed.

Data collection and analysis

Selection of studies

Two review authors (NP, SD) independently screened the abstract or title or both of each record retrieved by the literature searches to determine which studies should be assessed further. We obtained the full-text of all potentially relevant records and evaluated these for inclusion in the review. Any disagreements were resolved through consensus or by recourse to the review's advisory group. If we could not resolve a disagreement, we categorised the study as awaiting classification and contacted the study authors for clarification. We have presented an adapted PRISMA flow diagram illustrating the process of study selection (Liberati 2009). We described all articles excluded after full-text assessment and the reasons for their exclusion in a 'Characteristics of excluded studies' table.

Data extraction and management

For studies that fulfilled the inclusion criteria, two review authors (NP and SD/YB) independently extracted key information on participants, interventions, and comparators. We reported data on efficacy outcomes and adverse events using standardised data extraction sheets from the CMED Group. Any disagreements were resolved by discussion or by consulting with a member of the review's advisory group if required (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 15; Appendix 16).

We provided information about potentially relevant ongoing trials, including the trial identifiers, in the 'Characteristics of ongoing studies' table and in Appendix 9 'Matrix of study endpoint (publications and trial documents)'. We identified the protocol for each included study and reported primary, secondary, and other outcomes in comparison with the data in the publications in the Appendix 9.

We emailed the author of the ongoing trial to enquire as to whether they would be willing to answer questions regarding their trials. The results of this survey are presented in Appendix 14.

Dealing with duplicate and companion publications

In the case of duplicate publications, companion documents, or multiple reports of a primary study, we maximised the information yield by collating all available data and used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study identifier (ID) of the included study. Furthermore, we also listed duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers

If data from included studies were available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the study, we collated and critically appraised all available data. If an included study was marked as completed in a clinical trial register but no additional information (study results, publication, or both) was available, we added this study to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

Two review authors (NP, SD/YB) independently assessed the risk of bias for each included study. Any disagreements were resolved by consensus or by consulting a member of the review's advisory group to achieve consensus. If there was inadequate information in the publication, trial protocols, or other sources, we contacted the study authors for more detail and to request missing data on 'Risk of bias' domains.

We used the Cochrane 'Risk of bias' assessment tool (Higgins 2019b), assessing each domain as low, high, or unclear risk of bias (for details, see Appendix 3). We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein (Higgins 2019b).

Summary assessment of risk of bias

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure. We distinguished between self-reported, investigator-assessed, and adjudicated outcome measures.

We defined the following endpoints as self-reported or subjective outcomes.

- Adverse events, depending on measurement
- Health-related quality of life

We defined the following endpoints as investigator-assessed or objective outcomes.

- All-cause mortality
- Diabetes-related mortality
- Diabetes-related morbidity
- Incidence of type 2 diabetes
- HbA1c
- Adverse events, depending on measurement
- Socioeconomic effects

Risk of bias for a study across outcomes

Some 'Risk of bias' domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a study. In the case of high risk of selection bias, we marked all endpoints investigated in the associated study as high risk. Otherwise, we would not perform a summary assessment of the risk of bias across all outcomes for a study.

Risk of bias for an outcome within a study and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both study-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains; unclear risk to denote an unclear risk of bias for one or more key domains; and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across studies and across domains

To facilitate our assessment of the certainty of evidence for key outcomes, we assessed risk of bias across studies and domains for outcomes included in the 'Summary of findings' table. We assessed the evidence as being at low risk of bias when most information came from studies at low risk of bias; unclear risk of bias when most information came from studies at low or unclear risk of bias; and high risk of bias when a sufficient proportion of information came from studies at high risk of bias.

Measures of treatment effect

When at least two included studies were available for a comparison and a given outcome, dichotomous data were described as a risk ratio (RR) or odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes measured on the same scale (e.g. weight loss in kg), we estimated the intervention effect using the mean difference (MD) with 95% CI. For continuous outcomes that measured the same underlying concept (e.g. health-related quality of life) but used different measurement scales, we calculated the standardised mean difference (SMD). We expressed time-to-event data as a hazard ratio (HR) with 95% CI.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over studies, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same study was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants did not contribute multiply (splitting the 'shared' group into two or more groups). Whilst the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2019a).

We had planned to attempt to re-analyse cluster-RCTs that had not appropriately adjusted for clustering in their analyses. The variance of the intervention effects would have been inflated by a design effect. Calculation of a design effect involves estimation of an intracluster correlation coefficient (ICC). We would have obtained estimates of ICCs through contact with the study authors, or imputed them using estimates from other included studies that reported ICCs, or using external estimates from empirical research (e.g. Bell 2013). We had planned to examine the impact of clustering using sensitivity analyses and the approach described above. However, the included study adjusted for clustering adequately, and it was not necessary to re-analyse it.

Dealing with missing data

If possible, we obtained missing data from the authors of the included studies. We carefully evaluated important numerical data such as screened, randomly assigned participants as well as intention-to-treat (ITT) and as-treated and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up and withdrawals), and we critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

In studies where the standard deviation (SD) of the outcome was not available at follow-up or could not be re-created, we standardised by the average of the pooled baseline SD from those studies that reported this information. Where included studies did not report means and SDs for outcomes and the necessary information was unobtainable from the study authors, we imputed these values by estimating the mean and variance from the median, range, and size of the sample (Hozo 2005). We investigated the impact of imputation on meta-analyses by performing sensitivity analyses, and we reported for every outcome which studies had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical, methodological, or statistical heterogeneity, we would not report study results as the pooled effect estimate in a meta-analysis.

We would identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we would also consider the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). An I^2 statistic value of ≥ 75% indicates a considerable level of heterogeneity (Deeks 2019). Had we found heterogeneity, we would have attempted to determine the possible reasons for it by examining individual study and subgroup characteristics. However, given that only one study was included, heterogeneity was not assessed.

Assessment of reporting biases

We did not find enough studies to carry out an assessment of reporting biases. Had we included 10 or more studies that investigated a particular outcome, we would have used funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies), and publication bias (Sterne 2017).

Data synthesis

We planned to undertake (or display) a meta-analysis only if the participants, interventions, comparisons, and outcomes were sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across studies, we would primarily summarise data at low risk of bias using a random-effects model (Wood 2008). We would interpret random-effects meta-analyses with due consideration to the whole distribution of effects, ideally by presenting a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least three studies to be calculated and specifies a predicted range for the true treatment effect in an individual study (Riley 2011). For rare events such as event rates below 1%, we used the Peto's odds ratio method, provided that there was no substantial imbalance between intervention and comparator group sizes and intervention effects were not exceptionally large. We also performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019).

Subgroup analysis and investigation of heterogeneity

We did not conduct any subgroup analysis as only one study was included in the review. We expected the following characteristics to introduce clinical heterogeneity and planned to carry out subgroup analyses for these, including investigation of interactions (Altman 2003).

- Sex
- Ethnicity
- Diagnostic criteria for diabetes
- Use of different screening methods
- Age
- Presence of cardiovascular disease risk factors such as hypertension

Sensitivity analysis

We did not include enough studies to carry out sensitivity analysis. We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published studies
- Effect of risk of bias, as specified in the Assessment of risk of bias in included studies section
- Very long or large studies to establish the extent to which they dominated the results

We used of the following filters, if applicable: diagnostic criteria, imputation used, language of publication (English versus other languages), source of funding (industry versus other), or country (depending on data).

We also planned to test the robustness of results by repeating the analyses using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We presented the overall certainty for each outcome specified below according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) as well as external validity, such as directness of results. Two review authors (NP, SD) independently rated the certainty of the evidence for each outcome. Any differences in assessment were resolved by discussion or by consultation with a third review author (YB).

We included Appendix 15 'Checklist to aid consistency and reproducibility of GRADE assessments' to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we used the GRADEpro Guideline Development Tool (GDT) software and presented evidence profile tables as an appendix (GRADEpro GDT 2015). We presented results for outcomes as described in the Types of outcome measures section. When meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the certainty of trials by using footnotes, and made comments to aid the reader's understanding of the Cochrane Review where necessary.

'Summary of findings' table

We presented a summary of the evidence in the Summary of findings 1. This provides key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), employing along with Review Manager 5 software (RevMan 2014).

The intervention presented in the 'Summary of findings' table was invitation to screening for type 2 diabetes mellitus. The comparator was regular care (no invitation to screening for type 2 diabetes mellitus).

We reported the following outcomes, listed according to priority.

- All-cause mortality
- Diabetes-related mortality
- Diabetes-related morbidity
- Incidence of type 2 diabetes
- Health-related quality of life
- Adverse events
- Socioeconomic effects

RESULTS

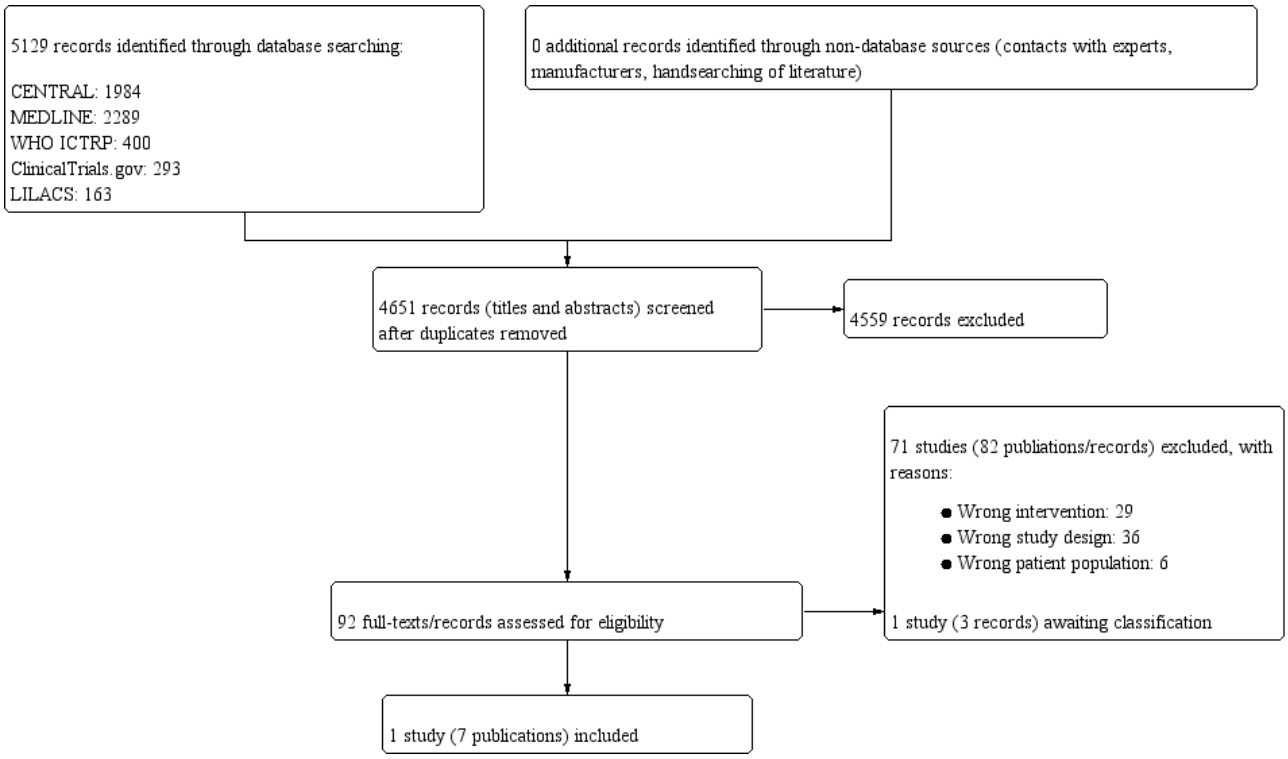
Description of studies

For a detailed description of studies, see Table 1; Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Two review authors screened the titles and abstracts of 4651 unique records identified through electronic database searching, of which 83 full-texts were assessed against the eligibility criteria. We excluded 71 studies (82 publications/records) with reasons: 29 studies did not include an eligible intervention, 36 were not RCTs, and six assessed the wrong patient population. We included seven records pertaining to one RCT. An additional 20 full-texts linked to this included study were identified in ClinicalTrials.gov; however, they did not address our review question. We assessed three records pertaining to one study as awaiting classification. Figure 1 outlines the study selection process.

Figure 1. Study flow diagram.



Included studies

For a detailed description of the characteristics of the included study, see Characteristics of included studies and Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13. The following is a succinct overview.

Source of data

We included one study, the ADDITION-Cambridge study, in the review (with six linked publications) (Simmons 2012). This trial was part of the larger multicentre ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) trial. The ADDITION trial included 334 general practices in the United Kingdom, the Netherlands, and Denmark (Lauritzen 2000). The general practices were randomised to a screening intervention for diabetes followed by routine care according to national guidelines for the control participants or multifactorial treatment for the intervention group. Men and women aged 40 to 69 years were eligible for inclusion. Individuals with known diabetes at the time of screening, women who were pregnant or lactating, those who were housebound or in poor health and unlikely to survive a year were excluded. In Denmark, participating primary care physicians forwarded diabetes-related information to all eligible individuals enrolled in their practices. An accompanying letter and questionnaire encouraged individuals at high risk for diabetes to undergo a blood glucose screening test. In England, a previously validated risk score using routine general practice data identified individuals at high risk for diabetes. In the Netherlands, all eligible participants were offered a screening test (Lauritzen 2000). In all three countries, random capillary blood glucose levels identified individuals with levels ≥ 5.5 mmol/L, who were then invited to undergo a fasting capillary blood glucose, and if needed, an OGTT. People newly diagnosed with diabetes were invited to participate in the study. The intensive therapy comprised a group of actions according to strict targets, as well as further randomisation where some participants were allocated to country-specific interventions. These included motivating adherence to lifestyle changes and medication. A trained facilitator delivered these interventions in England and the Netherlands, whilst trained practitioners did so in Denmark. The choice of medication was determined by the individual doctor and patient based on treatment effect, side-effects, and costs, with the aim of achieving treatment targets (Lauritzen 2000).

Whilst the ADDITION study was a multicentre study conducted in these three countries, data relevant data to this review were only available for the ADDITION-Cambridge centre. The ADDITION-Cambridge study was a pragmatic parallel group, cluster-randomised trial that involved 33 general practices in Eastern England. The study comprised two phases, of which the first phase that related to diabetes screening was relevant to this review. The second phase compared the effects of intensive multifactorial therapy with routine care in individuals who were diagnosed with screen-detected type 2 diabetes. The second phase was not relevant to this review, for which the focus was to evaluate screening as the intervention and not different treatment strategies to manage diabetes.

Results from database searches and in ClinicalTrials.gov registry record indicated many publications linked to the ADDITION-Cambridge study. Of these, some assessed results of the screening phase and others assessed results of phase 2. We excluded all publications linked to phase 2 (N = 33), which were not relevant to this review. Amongst publications linked to phase 1, which were relevant to this review and met the study design criteria,

we included seven publications. For example, of those excluded, one paper assessed anxiety and depression as adverse effects of screening outcomes in a convenient subgroup of screening practices and control practices part of the ADDITION trial (Eborall 2007; Echouffo-Tcheugui 2015). Another paper simply described the baseline cross-sectional data with no follow-up data presented (Sandbaek 2008), whilst Griffin 2012 described the impact of early intensive therapy on five-year outcomes in participants with screen-detected diabetes from all centres. Another study evaluated the impact of training general practitioners for intensive management of patients with screen-detected diabetes (Simmons 2017).

All data presented in this review were obtained from published literature.

Comparisons

Simmons 2012 compared inviting versus not inviting high-risk individuals to screening for diabetes.

Overview of study populations

The ADDITION-Cambridge study included 20,184 participants from 33 general practices in Eastern England (Simmons 2012). Of these, 27 practices were randomised to the intervention (screening) group, with 11,737 participants actually being screened, and 5 practices were randomised to the control (no screening) group, with 4137 participants. The numbers of participants finishing the study in both groups were not reported.

Study design

The ADDITION-Cambridge study was a pragmatic parallel-group, unbalanced cluster-randomised trial of screening, where 27 practices were randomised to the intervention (screening) arm and 5 practices were randomised to the comparison (no screening) group (Simmons 2012). The investigators assessing outcomes and analysing data were blinded to group assignment. The study started in November 2001 and continued until November 2011, with median follow-up of 9.6 years (interquartile range 8.9 to 9.9 years).

Settings

The ADDITION-Cambridge study was conducted in general primary care practices in Eastern England (Simmons 2012).

Participants

Participants included in the study were men and women registered with participating practices in Eastern England, who had a diabetes risk score of more than 0.17 before the start of the study but no known diabetes. The ethnic groups of participants were not reported. In both study arms 36% of participants were female. The mean age of participants in the screening group was 58.2 years, compared to 57.9 years in the no-screening group. Glycated haemoglobin A1c (HbA1c) and fasting capillary blood glucose (FBG) at baseline were not reported. Mean body mass index (BMI) was 30.5 kg/m^2 (SD 4.6) and 30.6 kg/m^2 (SD 4.6) in the intervention and control groups, respectively. Participants in the screening and no-screening groups were receiving antihypertensive medication (45.9% versus 44.8%) and prescribed steroids (5.4% and 3.7%) at baseline. Participants were excluded from the study if they were pregnant or lactating, had an illness with a likely prognosis of less than one year, or a psychiatric illness likely to limit study involvement.

Interventions

Simmons 2012 reported on the findings from the first phase of the ADDITION-Cambridge study, which assessed invitation to screening versus no invitation to screening for type 2 diabetes mellitus of participants at high-risk for diabetes. The diabetes risk score to identify high-risk individuals comprised variables relating to age, sex, body mass index, and the use of prescribed steroid and anti-hypertensive medication. The screening process involved stepwise screening of individuals at high-risk for undetected diabetes using random capillary blood glucose (RCBG), FBG, capillary HbA1c, and OGTT to confirm the results. RCBG, FBG, and OGTT were undertaken on different days.

Outcomes

The primary outcome measured in this study was all-cause mortality (Simmons 2012). Secondary outcomes assessed included mortality from cardiovascular disease, cancers, other causes, and diabetes-related mortality. Mortality was assessed through mortality surveillance by the England and Wales Office of National Statistics.

Excluded studies

We excluded 73 records after full-text screening. For further details see Characteristics of excluded studies.

Studies awaiting classification

We assessed one study (three records) as awaiting classification (Klijs 2012). This study is an RCT conducted in residents of two Dutch municipalities. A total of 10,609 individuals aged 40 to 74 years were randomised to either the diabetes screening or the control arm. The outcomes relevant to this review included: 1) evaluating the effectiveness of screening for type 2 diabetes; and 2) determining whether early detection and treatment of type 2 diabetes compared with no screening contributes to reducing and/or preventing related morbidity and mortality. This study is described as completed in the trial registry, but no publication details were available. We contacted the study author but have not received a response. The trial registry includes one available publication on this study; however, this was an analysis of a subset of participants of the main study by Klijs 2012, and the study design did not meet the criteria for inclusion in this review.

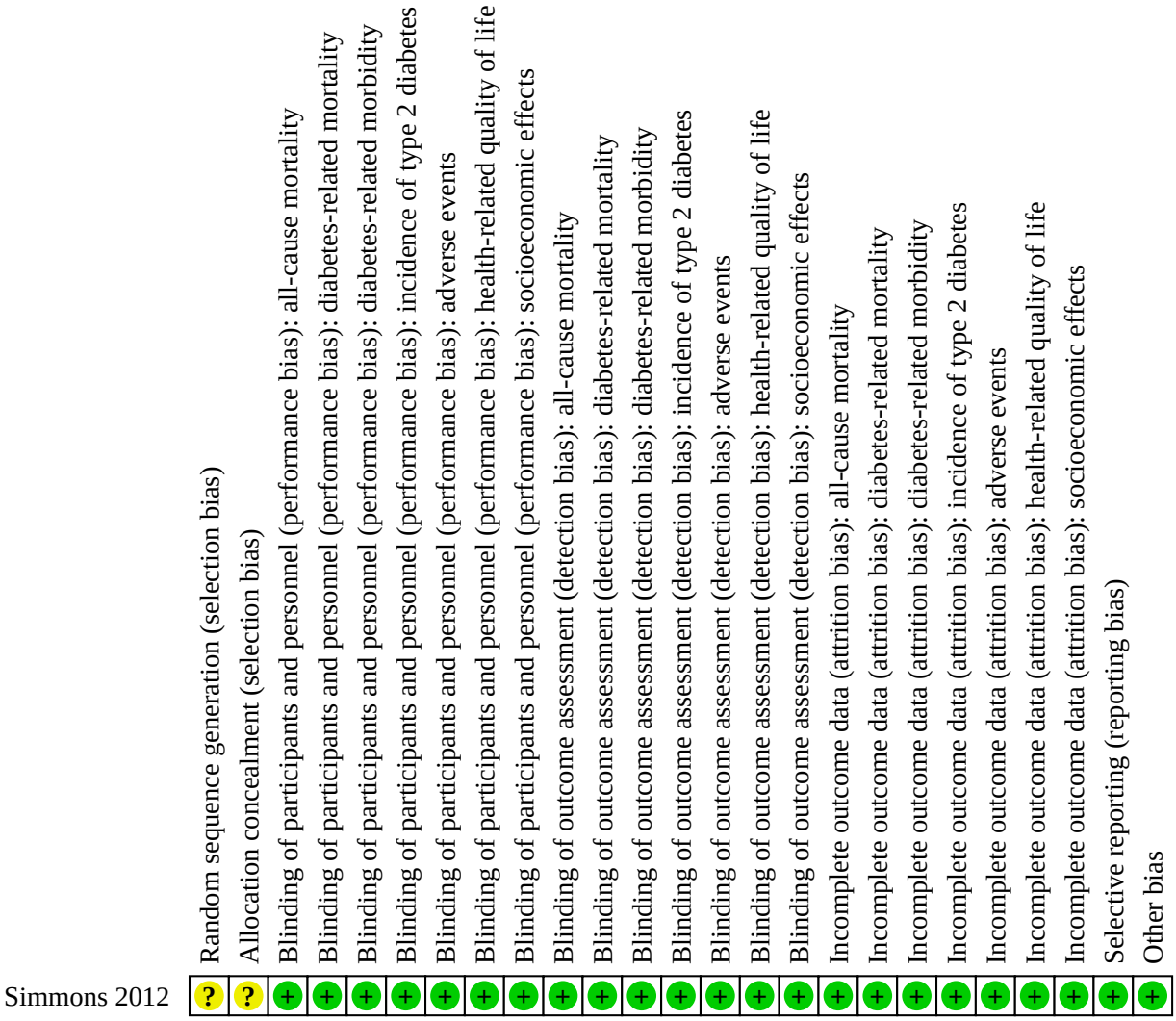
Risk of bias in included studies

For details on the risk of bias of the included study see Characteristics of included studies.

For an overview of review authors' judgements about each 'Risk of bias' item for the included study see Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (blank cells indicate that the particular outcome was not measured in the included study).

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (blank cells indicate that the particular outcome was not measured in the included study).



Allocation

A statistician used the method of minimisation to perform the randomisation, and there were no imbalances at baseline, either at the individual or cluster level. Allocation was concealed as the randomisation was done centrally. However, the included study was a cluster-RCT and randomised practices, therefore we assessed selection bias as unclear because it is unknown how and which participants were chosen in the practices to participate in the screening or no-screening intervention.

Blinding

It was not possible to blind participants or personnel in the ADDITION study. Knowing that you were screened may have altered the behaviour of participants; however, all-cause mortality and diabetes-related mortality, assessed through mortality surveillance by the England and Wales Office of National Statistics, are objective outcomes and are therefore not expected to be susceptible to lack of blinding. We thus classified these outcomes as being at low risk of performance bias and detection bias. However, as patient-reported outcomes, diabetes-related morbidity and health-related quality of life were judged to be at high risk of performance and detection bias.

Incomplete outcome data

All eligible participants were flagged for mortality surveillance by the England and Wales Office of National Statistics; the proportion of individuals lost to Office of National Statistics tracking was

equally distributed between study groups, and there was a very low loss to follow-up (1%). The study also used ITT analysis. It was thus classified as being at low risk of attrition bias.

However, for self-reported outcomes of diabetes-related morbidity and health-related quality of life, the risk of bias was high because of low response rates in the screening (62%) and control (53%) groups, with responders being different to non-responders at baseline. Responders were more likely to be older, female, on hypertensive medication, and have lower BMI and higher risk for undiagnosed diabetes compared with non-responders.

Selective reporting

All outcomes and methods were described as prespecified in the protocol, therefore we assessed the ADDITION-Cambridge study as being at low risk of reporting bias.

Other potential sources of bias

We assessed the ADDITION-Cambridge study as at low risk for other bias. Risk of recruitment bias was low as randomisation was done at the cluster level, and individual participants already belonged to the practices. The study accounted for clustering of practices correctly in their analysis. No other sources of bias were identified.

Effects of interventions

See: **Summary of findings 1** Screening for type 2 diabetes mellitus

Baseline characteristics

For details of baseline characteristics, see Appendix 6; Appendix 7.

The ADDITION-Cambridge study included individuals at high risk for diabetes. High risk in this study was determined using a simple previously validated risk score (diabetes risk score > 0.17). This included routine general practice data (age, gender, prescribed medication, and BMI) collected from their computerised medical records to identify people at high risk of having prevalent undiagnosed diabetes. Practices were eligible to take part if they could provide data for calculation of the risk score for at least 70% of their patients.

The percentage of female participants was 36% in both the intervention and control groups. The mean age and BMI in both groups was similar: 58.2 (SD 7.7) and 57.9 (SD 7.8) years old in the screened and control groups; and 30.5 (SD 4.6) and 30.6 (SD 4.6) kg/m^2 in the screened and control groups. In both groups about 45% of participants were receiving antihypertensive medication, and slightly more participants in the screened group were receiving prescribed steroids (5.4% versus 3.7%).

Screening versus no screening for type 2 diabetes

Primary outcomes

All-cause mortality

Simmons 2012 reported that screening compared to no screening for type 2 diabetes made no substantial difference to all-cause mortality at 10-year follow-up (hazard ratio (HR) 1.06, 95% confidence interval (CI) 0.90 to 1.25; P = 0.49; 20,184 participants; low-certainty evidence; Analysis 1.1). The number of deaths was 377 out of 4137 participants in the no-screening group and 1532 out of 15,089 participants invited for screening (11,737 participants attending screening). The rate per 1000 person-years was 9.89 (95% CI 8.94 to 10.94) in the no-screening group and 10.50 (95% CI 9.99 to 11.04) in the screening group.

Diabetes-related mortality

Diabetes-related mortality was described in our protocol as death from IHD or stroke. The ADDITION-Cambridge study noted whether diabetes was included anywhere on the death certificates (Simmons 2012). Screening compared to no screening for type 2 diabetes resulted in an HR of 1.26, 95% CI 0.75 to 2.12; 20,184 participants; low-certainty evidence; Analysis 1.2.

Simmons 2012 also reported that screening compared to no screening had no substantial impact on cardiovascular mortality (HR 1.02, 95% CI 0.75 to 1.39; Analysis 1.3), defined according to the International Classification of Diseases, 10th edition (ICD-10) code using I00–I99.

Simmons 2012 also reported that screening compared to no screening had no substantial impact on cancer mortality (HR 1.08, 95% CI 0.90 to 1.30; Analysis 1.4)

Diabetes-related morbidity

Simmons 2012 reported no substantial difference in self-reported cardiovascular events (stroke, IHD) between screening and no screening for type 2 diabetes at seven-year follow-up in a subsample (15% of participants in the screening group and 40% of participants in the control group) of the main ADDITION trial (odds ratio 0.90, 95% CI 0.71 to 1.15; 1945 participants).

Secondary outcomes

Incidence of type 2 diabetes

This outcome was not reported.

HbA1c

This outcome was not reported.

Adverse events

This outcome was not reported.

Health-related quality of life

Health-related quality of life was investigated in a subsample only. The response rate was 62% in the screening group and 53% in the control group.

Simmons 2012 reported no substantial difference in self-reported health-related quality of life between the intervention and control groups for type 2 diabetes (mean difference (MD) 0.002, 95% CI −0.02 to 0.02; 1945 participants). This was measured using the EuroQol (EQ-5D) generic health-related quality of life instrument, which comprises five questions on mobility, self-care, pain, usual activities, and psychological status with three possible answers for each item (1 = no problem, 2 = moderate problem, 3 = severe problem). The score ranges from −0.3 to 1, with the maximum score of 1 indicating the best health state.

Simmons 2012 reported no substantial difference in self-reported mental health between the intervention and control groups at seven-year follow-up (MD −0.38, 95% CI −1.33 to 0.57; 1945 participants). Mental health was measured using the 8-item Short Form Health Survey (SF-8) summary score, which assesses psychological distress and well-being (Echouffo-Tcheugui 2015) .

Socioeconomic effects

This outcome was not reported.

DISCUSSION

Summary of main results

The evidence from a single included study demonstrates that there is no substantial difference in all-cause and diabetes-related mortality over a 10-year period between participants at high-risk for diabetes who were either screened (intervention) once or not screened (control) for diabetes.

Overall completeness and applicability of evidence

Although the evidence shows that screening versus no screening for diabetes does not significantly impact all-cause and diabetes-related mortality, conclusions should not be drawn from a single study regarding these specific outcomes. The ADDITION-Cambridge study presented separate outcomes pertaining to cardiovascular- and diabetes-related mortality, which we have reported as such. However, this differs from our protocol, where we included death from IHD or stroke (i.e. cardiovascular outcomes) as diabetes-related mortality.

Diabetes-related morbidity was also a primary outcome in this review, which included IHD and stroke. These were self-reported in a substudy of the ADDITION-Cambridge trial (Simmons 2012). No substantial differences in cardiovascular events were noted. Other diabetes-related morbidity outcomes pertaining to microvascular complications such as diabetic retinopathy, diabetic nephropathy, or diabetic neuropathy were not reported in the screening and control groups.

Other secondary outcomes of interest were not reported in the ADDITION-Cambridge study, including incidence of type 2 diabetes, adverse events, HbA1c levels, and socioeconomic effects.

The participants in the ADDITION-Cambridge trial were all from the same setting, that is primary care practices in the United Kingdom. Consequently, this review cannot provide evidence for effects of screening in other settings, such as low- and middle-income countries, for example.

Quality of the evidence

We included one large study with few methodological limitations in the review. We assessed the certainty of evidence for all-cause mortality and diabetes-related mortality to be low, downgrading because of serious imprecision, as the benefits ranged from beneficial to harmful.

Potential biases in the review process

Three review authors without financial interest in the outcome independently extracted data. None of these authors was involved in a previous review related to this topic. The review authors believe that an unbiased process was followed for this review. We consulted with the review's advisory group and other methods experts regarding the study selection process. This included a decision to exclude substudies of the included study, which addressed some of the review's outcomes of interest but did not meet the study design criteria for eligibility.

We contacted an author of a study that we assessed as awaiting classification but have received no response; it is therefore possible that a relevant study that could have provided evidence to address the review's objectives was not included in the review.

The original protocol was published in 2005. The current author team revised the protocol with the Review Group when it took over the review conduct from the previous author team. There have been no deviations from the protocol as agreed with the Review Group at that stage.

Agreements and disagreements with other studies or reviews

In a report for the US Preventive Services Task Force, Selph 2015, and in a health-assessment technology report for the National Screening Committee (Waugh 2013), screening for diabetes made no difference in mortality at 10 years compared to no screening. Both reports included two studies that addressed this question, one of which was included in this review (Simmons 2012), and the other which was excluded, as it did not meet our study design criteria (Simmons 2011). We are unaware of other reviews on this specific topic.

The Danish arm of the ADDITION-Europe study, which we did not include in our review because it was a non-randomised controlled study, compared the risk of mortality and cardiovascular events in individuals with incident diabetes in the screening and control groups (Simmons 2017b_ADDITION Denmark). This study reported reduced all-cause mortality, diabetes-related mortality, and cardiovascular events in the screening compared to the no-screening group.

The same study examined the effect of screening for diabetes and cardiovascular risk factors on population-level mortality rates and cardiovascular events (Simmons 2017a_ADDITION Denmark). There was no significant difference between the screening and no-screening groups in all-cause mortality, cardiovascular mortality, diabetes-related mortality, or first cardiovascular event.

The Inter99 was an RCT conducted in Copenhagen, Denmark to examine the effect of invitation to participate in a screening and lifestyle programme on IHD; diabetes incidence was a secondary outcome (Lau 2016). We excluded this study because the intervention differed from that prespecified in our protocol, which assessed the effect of screening for diabetes only. Lau 2016 reported no significant difference in the incidence of diabetes between groups at 10-year follow-up.

The Ely Study, which we did not include in our review because it was not an RCT, compared outcomes in individuals invited and not invited for diabetes screening. Participants who were invited for screening compared with those not invited for screening had a non-significant 21% reduction in all-cause mortality after a median 10 years' follow-up (Simmons 2011). The prevalence of self-reported heart attack and stroke, and self-rated health was similar in individuals without diabetes in the screened and unscreened groups of the Ely cohort 13 years after commencement of screening (Simmons 2011).

AUTHORS' CONCLUSIONS

Implications for practice

We are uncertain about the effects of screening for diabetes on all-cause mortality and diabetes-related mortality. We included evidence from one study only, therefore we could draw no firm conclusions relating to the health outcomes of early type 2 diabetes screening. Furthermore, the included study did not assess all the outcomes we intended to address in the review: diabetes-related morbidity, incidence of type 2 diabetes, health-related quality of life, adverse events, and socioeconomic effects.

Implications for research

This systematic review found only one study that fulfilled the review criteria. Possible reasons for this may be the costs involved in conducting trials on this topic, which would require following a large sample of participants for a prolonged time period. The aim would be to not only determine the incidence of diabetes in the intervention and control groups but also to determine the incidence of diabetes-related morbidity and mortality, which usually develop over at least 5 to 10 years. Nevertheless, more evidence pertaining to the effects of diabetes screening is required. Outcomes of importance for which more evidence is required include diabetes-related morbidity, diabetes-related cardiovascular mortality, diabetes incidence in high-risk populations, and impact of diabetes screening on well-being and socioeconomic outcomes, which were not reported in the included study. Some of these outcomes were reported in substudies of the included study, but due to these being substudies of the main study, following different methodology, they were not eligible for inclusion. More study evidence on the effects of screening in other settings, such as in low- and middle-income countries for example, is also required.

ACKNOWLEDGEMENTS

The first protocol for this Cochrane Review was published by Woolthuis EK, de Grau W, van de Laar F, and Akkermans R. We also thank Dagmar Haller, Johanna Sommer, Arabelle Rieder, Catherine Herter-Clavel, Anca Paschoud, Danilo Janjic, Angel Vilaseca, Cédric Gillabert, Wim JC De Grauw, and Christophe Combescure for their work on the protocol update. We would like to thank the review advisory board for their input in the review: Tamara Kredo, Taryn Young, and Andre Pascal Kengne. We thank Maria-Inti Metzendorf, Information Specialist for Cochrane Metabolic and Endocrine Disorders (CMED), for the development of the search strategy. The review authors and the CMED editorial base are grateful to the peer reviewer Philippa Middleton, SAHMRI and The University of Adelaide, Australia, for her time and comments.

REFERENCES

References to studies included in this review

Simmons 2012 *{published data only}*

Echouffo-Tcheugui JB, Simmons RK, Prevost AT, Williams KM, Kinmonth AL, Wareham NJ, et al. Long-term effect of population screening for diabetes on cardiovascular morbidity, self-rated health, and health behavior. *Annals of Family Medicine* 2015;**13**(2):149-57. [PMID: 25755036]

Echouffo-Tcheugui JB, Simmons RK, Williams KM, Barling RS, Prevost AT, Kinmonth AL, et al. The ADDITION-Cambridge trial protocol: a cluster-randomised controlled trial of screening for type 2 diabetes and intensive treatment for screen-detected patients. *BMC Public Health* 2009;**9**:136. [PMID: 19435491]

Griffin S. A single screening for type 2 diabetes in high-risk adults did not reduce mortality over 10 years. *Annals of Internal Medicine* 2013;**158**:JC4.

Sandbaek A, Griffin SJ, Rutten G, Davies M, Stolk R, Khunti K, et al. Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia* 2008;**51**(7):1127-34. [PMID: 18443762]

Simmons RK, Borch-Johnsen K, Lauritzen T, Rutten GE, Sandbaek A, van den Donk M, et al. A randomised trial of the effect and cost-effectiveness of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with screen-detected type 2 diabetes: the Anglo-Danish-Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION-Europe) study. *Health Technology Assessment (Winchester, England)* 2016;**20**(64):1-86. [PMID: 27583404]

Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, Sargeant LA, Williams KM, Prevost AT, et al. Effect of screening for type 2 diabetes on population mortality over ten years: the ADDITION-Cambridge cluster-randomised controlled trial. *Diabetologia* 2012;**55**:S81-2.

* Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, Sargeant LA, Williams KM, Prevost AT, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. *Lancet* 2012;**380**(9855):1741-8. [PMID: 23040422]

References to studies excluded from this review

Acosta 2018 *{published data only}*

Acosta T, Barengo NC, Arrieta A, Ricaurte C, Tuomilehto JO. A demonstration area for type 2 diabetes prevention in Barranquilla and Juan Mina (Colombia): baseline characteristics of the study participants. *Medicine* 2018;**97**(1):e9285.

ACTRN12611000518965 *{published data only}*

ACTRN12611000518965. Achieving diabetes action and collaborative change - a cluster RCT in Aboriginal health [In Aboriginal and Torres Strait Islander peoples can a Aboriginal primary health service collaborative intervention increase screening and management of type 2 diabetes when compared with usual care]. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336935 (first received 18 May 2011).

ACTRN12616001240437 *{published data only}*

ACTRN12616001240437. The pharmacy diabetes screening trial: a comparison of three community pharmacy based approaches to screening for type 2 diabetes on proportions of newly diagnosed type 2 diabetes cases. anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12616001240437 (first received 6 September 2016).

ADDITION-Leicester 2015 *{published data only}*

Bodicoat DH, O'Donovan G, Dalton AM, Gray LJ, Yates T, Edwardson C, et al. The association between neighbourhood greenspace and type 2 diabetes in a large cross-sectional study. *BMJ Open* 2014;**4**(12):e006076.

Gray LJ, Yates T, Davies MJ, Brady E, Webb DR, Sattar N, et al. Defining obesity cut-off points for migrant South Asians. *PLOS ONE* 2011;**6**(10):e26464.

Kidy FF, Dhalwani N, Harrington DM, Gray LJ, Bodicoat DH, Webb D, et al. Associations between anthropometric measurements and cardiometabolic risk factors in white European and South Asian adults in the United Kingdom. *Mayo Clinic Proceedings* 2017;**92**(6):925-33.

Mostafa SA, Davies MJ, Morris DH, Yates T, Srinivasan BT, Webb D, et al. The association of the triglyceride-to-HDL cholesterol ratio with insulin resistance in White European and South Asian men and women. *PLOS ONE* 2012;**7**(12):e50931.

Mostafa SA, Davies MJ, Webb DR, Srinivasan BT, Gray LJ, Khunti K. Independent effect of ethnicity on glycemia in South Asians and white Europeans. *Diabetes Care* 2012;**35**(8):1746-8.

Mostafa SA, Khunti K, Kilpatrick ES, Webb D, Srinivasan BT, Gray LJ, et al. Diagnostic performance of using one- or two-HbA1c cut-point strategies to detect undiagnosed type 2 diabetes and impaired glucose regulation within a multi-ethnic population. *Diabetes & Vascular Disease Research* 2013;**10**(1):84-92.

NCT00318032. A study to investigate the benefits of the early detection and intensive treatment of type 2 diabetes. clinicaltrials.gov/show/NCT00318032 (first received 25 April 2006).

Webb D, Dales J, Zaccardi F, Hill S, Moore C, Farooqi A, et al. Intensive versus standard multifactorial cardiovascular risk factor control in screen-detected type 2 diabetes: 5-year and longer-term modelled outcomes of the ADDITION-Leicester study. *Diabetes/Metabolism Research and Reviews* 2019;**35**(3):e3111.

Webb DR, Gray LJ, Khunti K, Srinivasan B, Taub N, Campbell S, et al. Screening for diabetes using an oral glucose tolerance test within a western multi-ethnic population identifies modifiable cardiovascular risk: the ADDITION-Leicester study. *Diabetologia* 2011;**54**(9):2237-46.

Webb DR, Khunti K, Srinivasan B, Gray LJ, Taub N, Campbell S, et al. Rationale and design of the ADDITION-Leicester study, a systematic screening programme and randomised controlled trial of multi-factorial cardiovascular risk intervention in people with type 2 diabetes mellitus detected by screening. *Trials* 2010;**11**:16.

Black 2014 *{published data only}*

Black JA, Sharp SJ, Wareham NJ, Sandbaek A, Rutten GE, Lauritzen T, et al. Does early intensive multifactorial therapy reduce modelled cardiovascular risk in individuals with screen-detected diabetes? Results from the ADDITION-Europe cluster randomized trial. *Diabetic Medicine* 2014;**31**(6):647-56.

Black 2015 *{published data only}*

Black JA, Long GH, Sharp SJ, Kuznetsov L, Boothby CE, Griffin SJ, et al. Change in cardio-protective medication and health-related quality of life after diagnosis of screen-detected diabetes: results from the ADDITION-Cambridge cohort. *Diabetes Research & Clinical Practice* 2015;**109**(1):170-7.

Charles 2011 ADDITION *{published data only}*

Charles M, Ejskjaer N, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A. Prevalence of neuropathy and peripheral arterial disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. *Diabetes Care* 2011;**34**(10):2244-9. [PMID: 21816977]

Charles 2013 ADDITION *{published data only}*

Charles M, Fleischer J, Witte DR, Ejskjaer N, Borch-Johnsen K, Lauritzen T, et al. Impact of early detection and treatment of diabetes on the 6-year prevalence of cardiac autonomic neuropathy in people with screen-detected diabetes: ADDITION-Denmark, a cluster-randomised study. *Diabetologia* 2013;**56**(1):101-8. [PMID: 23064291]

Charles 2017 ADDITION *{published data only}*

Charles M, Skriver MV, Griffin SJ, Simmons RK, Witte DR, Dalsgaard EM, et al. Does training and support of general practitioners in intensive treatment of people with screen-detected diabetes improve medication, morbidity and mortality in people with clinically-diagnosed diabetes? Investigation of a spill-over effect in a cluster RCT. *PLOS ONE* 2017;**12**(2):e0170697. [PMID: 28151941]

ChiCTR1800015274 *{published data only}*

ChiCTR1800015274. Research on the effect of early diabetes screening and intervention on pregnancy outcome in pregnant women with high risk of diabetes. www.chictr.org.cn/showprojen.aspx?proj=26002 (first received 20 March 2018).

ChiCTR1800017260 *{published data only}*

ChiCTR1800017260. Screening for people at risk for type 2 diabetes. apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800017260 (first received 6 July 2018).

CTRI/2016/09/007323 *{published data only}*

CTRI/2016/09/007323. Screening and prevention of non communicable diseases (NCDs) through schools and community based approach. www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=12512&EncHid=&modid=&compid=%27,%2712512det%27 (first received 29 September 2016).

CTRI/2017/10/010199 *{unpublished data only}*

CTRI/2017/10/010199. Diabetes and tuberculosis - integrated management using the primary healthcare infrastructure in India [Integrated chronic disease management using the primary healthcare infrastructure in India – a feasibility]. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=15771&EncHid=&userName=CTRI/2017/10/010199 (first received 25 October 2017).

CTRI/2018/08/015536 *{published data only}*

CTRI/2018/08/015536. Global health research for cardiovascular disease and diabetes. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=28022&EncHid=&userName=CTRI/2018/08/015536 (first received 30 August 2018).

CTRI/2018/08/015568 *{published data only}*

CTRI/2018/08/015568. Research to practice an ideal screening model for complication of diabetes in India. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=27990&EncHid=&userName=CTRI/2018/08/015568 (first received 31 August 2018).

CTRI/2018/12/016532 *{unpublished data only}*

CTRI/2018/12/016532. e health initiatives for health. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=27309&EncHid=&userName=CTRI/2018/12/016532 (first received 5 December 2018).

Dalsgaard 2010 ADDITION Denmark *{published data only}*

* Dalsgaard EM, Christensen JO, Skriver MV, Borch-Johnsen K, Lauritzen T, Sandbaek A. Comparison of different stepwise screening strategies for type 2 diabetes: finding from Danish general practice, Addition-DK. *Primary Care Diabetes* 2010;**4**(4):223-9. [PMID: 20675208]

Dalsgaard 2014 ADDITION *{published data only}*

Dalsgaard EM, Vestergaard M, Skriver MV, Borch-Johnsen K, Lauritzen T, Sandbaek A. Socioeconomic position and cardiovascular risk factors among people with screen-detected type 2 DM: six-year follow-up of the ADDITION-Denmark trial. *Primary Care Diabetes* 2014;**8**(4):322-9. [PMID: 24613817]

den Ouden 2015 ADDITION *{published data only}*

den Ouden H, Berends J, Stellato RK, Beulens JW, Rutten GE. Effect of six years intensified multifactorial treatment on levels of hs-CRP and adiponectin in patients with screen detected type 2 diabetes: the ADDITION-Netherlands randomized trial. *Diabetes/Metabolism Research and Reviews* 2015;**31**(7):758-66. [PMID: 26109470]

DRKS00009837 *{unpublished data only}*

DRKS00009837. Diabetes mellitus screening for ambulant an in hospital patients - feasibility study [Diabetes mellitus screening bei stationären und ambulanten Patienten - Machbarkeitsstudie]. www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00009837 (first received 25 February 2016).

Dunkley 2017 *{published data only}*

Dunkley AJ, Tyrer F, Spong R, Gray LJ, Gillett M, Doherty Y, et al. Screening for glucose intolerance and development of a lifestyle education programme for prevention of type 2 diabetes in a population with intellectual disabilities: the STOP Diabetes research project. In: NIHR Journals Library. National Library of Medicine, National Institutes of Health, 2017.

Eborall 2007 ADDITION *{published data only}*

Eborall HC, Griffin SJ, Prevost AT, Kinmonth AL, French DP, Sutton S. Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. *BMJ* 2007;**335**(7618):486.

Griffin 2011 ADDITION *{published data only}*

Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbaek A, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet (London, England)* 2011;**378**(9786):156-67. [PMID: 21705063]

Harris 2003 *{published data only}*

Harris RP, Lux LJ, Bunton AJ, Sutton SF, Lohr KN, Donahue KP, et al. Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2003;**138**:215-29.

Hellgren 2015 *{published data only}*

Hellgren M, Daka B, Larsson C. HbA1c is not enough in screening for impaired glucose metabolism. Glucose tolerance tests are also needed, as shown in Swedish prospective epidemiological study. *Lakartidningen* 2015;**112**:29.

Herman 2015 *{published data only}*

Herman WH, Ye W, Griffin SJ, Simmons RK, Davies MJ, Khunti K, et al. Early detection and treatment of type 2 diabetes reduce cardiovascular morbidity and mortality: a simulation of the results of the Anglo-Danish-Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION-Europe). *Diabetes Care* 2015;**38**:1449-55.

ISRCTN21333761 *{published data only}*

ISRCTN21333761. Better prevention and screening: personalized clinical visits for adults. www.isrctn.com/ISRCTN21333761 (first received 31 August 2016).

ISRCTN57962668 *{published data only}*

ISRCTN57962668. Multi-centre risk-based screening for diabetes and its complications. www.isrctn.com/ISRCTN57962668 (first received 18 August 2018).

Johansen 2012 ADDITION *{published data only}*

Johansen NB, Charles M, Vistisen D, Rasmussen SS, Wiinberg N, Borch-Johnsen K, et al. Effect of intensive multifactorial treatment compared with routine care on aortic stiffness and central blood pressure among individuals with screen-detected type 2 diabetes: the ADDITION-Denmark study. *Diabetes Care* 2012;**35**(11):2207-14. [PMID: 22787176]

Juul 2009 ADDITION *{published data only}*

Juul L, Sandbaek A, Foldspang A, Frydenberg M, Borch-Johnsen K, Lauritzen T. Adherence to guidelines in people with screen-detected type 2 diabetes, ADDITION, Denmark. *Scandinavian Journal of Primary Health Care* 2009;**27**(4):223-31. [PMID: 19929182]

Kenealy 2007 *{published data only}*

Kenealy T, Elley CR, Arroll B. Screening for diabetes and prediabetes. *Lancet* 2007;**370**:1888-9.

Kolaczynski 2000 *{published data only}*

Kolaczynski JW. Comments on type 2 diabetes screening and treatment. *American Family Physician* 2000;**61**:49-50.

Kullgren 2017 *{published data only}*

* Kullgren JT, Youles B, Shetty S, Richardson C, Fagerlin A, Heisler M. Forging new paths in diabetes prevention (FINDIT): study protocol for a randomized controlled trial. Trials 2017;**18**:167. [DOI: 10.1186/s13063-017-1887-6]

Kumar 2015 *{published data only}*

Kumar S, Shewade HD, Vasudevan K, Durairaju K, Santhi VS, Sunderamurthy B, et al. Effect of mobile reminders on screening yield during opportunistic screening for type 2 diabetes mellitus in a primary health care setting: a randomized trial. *Preventive Medicine Reports* 2015;**2**:640-4.

Kuznetsov 2015 ADDITION *{published data only}*

Kuznetsov L, Simmons RK, Sandbaek A, Maindal HT. The impact of intensive multifactorial treatment on perceptions of chronic care among individuals with screen-detected diabetes: results from the ADDITION-Denmark trial. *International Journal of Clinical Practice* 2015;**69**(4):466-73. [PMID: 25382351]

Lau 2016 *{published data only}*

Lau CJ, Pisinger C, Husemoen LLN, Jacobsen RK, Linneberg A, Jorgensen T, et al. Effect of general health screening and lifestyle counselling on incidence of diabetes in general population: inter99 randomised trial. *Preventive Medicine* 2016;**91**:172-9.

Lauritzen 2000 ADDITION *{published data only}*

Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity* 2000;**24 Suppl 3**:S6-11. [PMID: 11063279]

Lauritzen 2011 ADDITION *{published data only}*

Lauritzen T, Sandbaek A, Skriver MV, Borch-Johnsen K. HbA1c and cardiovascular risk score identify people who may benefit from preventive interventions: a 7 year follow-up of a high-risk screening programme for diabetes in primary care (ADDITION), Denmark. *Diabetologia* 2011;**54**(6):1318-26. [PMID: 21340624]

Law 2018 *{published data only}*

Law V, Featherstone T, Eurich DT, Simpson SH. Knowledge of a diabetes risk score does not alter diabetes screening practice in a seniors population: a randomized controlled trial. *Journal of the American Medical Directors Association* 2018;**19**(11):1021-3.

Maindal 2013 ADDITION *{published data only}*

Maindal HT, Toft U, Lauritzen T, Sandbaek A. Three-year effects on dietary quality of health education: a randomized controlled trial of people with screen-detected dysglycaemia (The ADDITION study, Denmark). *European Journal of Public Health* 2013;**23**(3):393-8. [PMID: 23132875]

Monti 2012 *{published data only}*

Monti LD, Lucotti PC, Setola E, Rossodivita A, Pala MG, Galluccio E, et al. Effects of chronic elevation of atrial natriuretic peptide and free fatty acid levels in the induction of type 2 diabetes mellitus and insulin resistance in patients with mitral valve disease. *Nutrition, Metabolism and Cardiovascular Diseases: NMCD* 2012;**22**(1):58-65. [PMID: 20709514]

NCT00007696 *{published data only}*

NCT00007696. Finding diabetes mellitus among veterans [CSP #705D - Screening for diabetes mellitus in veterans]. clinicaltrials.gov/ct2/show/NCT00007696 (first received 4 January 2001).

NCT00042042 *{published data only}*

NCT00042042. Screening adolescents for type 2 diabetes mellitus in a community clinic. clinicaltrials.gov/ct2/show/NCT00042042 (first received 23 July 2002).

NCT00253240 *{published data only}*

NCT00253240. Diabetes screening, risk management and disease management in a high-risk mental health population. clinicaltrials.gov/show/NCT00253240 (first received 15 November 2005).

NCT00377117 *{published data only}*

NCT00377117. Diabetes screening, risk management and disease management in a high-risk mental health population part II. clinicaltrials.gov/ct2/show/NCT00377117 (first received 15 September 2006).

NCT01591525 *{published data only}*

NCT01591525. Diabetes mellitus community based screening in minority populations. clinicaltrials.gov/ct2/show/NCT01591525 (first received 4 May 2012).

NCT02223793 *{published data only}*

NCT02223793. Effects of cardiovascular risk screening in pharmacies: a randomized study. clinicaltrials.gov/ct2/show/NCT02223793 (first received 22 August 2014).

NCT02418637 *{published data only}*

NCT02418637. Pilot study testing feasibility of health screening at farm site. clinicaltrials.gov/show/NCT02418637 (first received 16 April 2015).

NCT02513277 *{published data only}*

NCT02513277. Diabetes screening & prevention for people with learning (intellectual) disabilities: STOP diabetes study. [Screening for glucose intolerance and development of a lifestyle education programme for prevention of type 2 diabetes in a population with learning disabilities]. clinicaltrials.gov/ct2/show/NCT02513277 (first received 31 July 2015).

NCT02750527 *{published data only}*

NCT02750527. Pediatric population screening for type 1 diabetes and familial hypercholesterolemia in Lower Saxony, Germany (Fr1dolin). clinicaltrials.gov/ct2/show/NCT02750527 (first received 25 April 2016).

NCT03254979 *{published data only}*

NCT03254979. Optimizing the Primary Prevention of Type-2 Diabetes in Primary Health Care (PREDIAPS) [How to Engage Primary Health Care Providers in an Inter-professional Collaborative Modeling Processfor the Optimization of Type-2 Diabetes Primary Prevention: a Randomized Hybrid Implementation Trial]. https://clinicaltrials.gov/ct2/show/NCT03254979 21 August 2017.

NCT03395509 *{published data only}*

NCT03395509. The intersectional Viborg screening program: cost-(effectiveness) of screening for diabetes and cardiovascular diseases (VISP). clinicaltrials.gov/ct2/show/NCT03395509 (first received 10 January 2018).

Park 2008 *{published data only}*

Park P, Simmons RK, Prevost AT, Griffin SJ. Screening for type 2 diabetes is feasible, acceptable, but associated with increased short-term anxiety: a randomised controlled trial in British general practice. *BMC Public Health* 2008;**8**:350.

Raikou 2003 *{published data only}*

Raikou M, McGuire A. The economics of screening and treatment in type 2 diabetes mellitus. *Pharmacoeconomics* 2003;**21**:543-64.

Rasmussen 2016 *{published data only}*

Rasmussen SS, Johansen NB, Witte DR, Borch-Johnsen K, Sandbaek A, Lauritzen T, et al. Incidence of register-based diabetes 10 years after a stepwise diabetes screening programme: the ADDITION-Denmark study. *Diabetologia* 2016;**59**(5):989-97.

Reid 1974 *{published data only}*

Reid DD, Brett GZ, Hamilton PJ, Jarrett RJ, Keen H, Rose G. Cardiorespiratory disease and diabetes among middle-aged male Civil Servants. A study of screening and intervention. *Lancet* 1974;**1**:469-73.

Rubak 2009 ADDITION *{published data only}*

Rubak S, Sandbaek A, Lauritzen T, Borch-Johnsen K, Christensen B. General practitioners trained in motivational interviewing can positively affect the attitude to behaviour change in people with type 2 diabetes. One year follow-up of an RCT, ADDITION Denmark. *Scandinavian Journal of Primary Health Care* 2009;**27**(3):172-9. [PMID: 19565411]

Scherstén 1966 *{published data only}*

Scherstén B. Health control. VI. Evaluation of screening methods for diabetes. *Lakartidningen* 1966;**63**:2659-64. [PMID: 5922329]

Simmons 2011 *{published data only}*

Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. Effect of screening for Type 2 diabetes on population level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort. *Diabetic Medicine* 2012;**29**:886-92.

Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. *Diabetologia* 2012;**55**:1651-9.

* Simmons RK, Rahman M, Jakes RW, Yuyun MF, Niggebrugge AR, Hennings SH, et al. Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort. *Diabetologia* 2011;**54**:312-9.

Simmons 2012b ADDITION *{published data only}*

Simmons RK, Sharp SJ, Sandbaek A, Borch-Johnsen K, Davies MJ, Khunti K, et al. Does early intensive multifactorial treatment reduce total cardiovascular burden in individuals with screen-detected diabetes? Findings from the ADDITION-Europe cluster-randomized trial. *Diabetic Medicine* 2012;**29**(11):e409-16.

Simmons 2014 ADDITION *{published data only}*

Simmons RK, Carlsen AH, Griffin SJ, Charles M, Christiansen JS, Borch-Johnsen K, et al. Variation in prescribing of lipid-lowering medication in primary care is associated with incidence of cardiovascular disease and all-cause mortality in people with screen-detected diabetes: findings from the ADDITION-Denmark trial. *Diabetic Medicine: a Journal of the British Diabetic Association* 2014;**31**(12):1577-85. [PMID: 25185778]

Simmons 2017a_ADDITION Denmark *{published data only}*

Simmons RK, Griffin SJ, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A. Effect of population screening for type 2 diabetes and cardiovascular risk factors on mortality rate and cardiovascular events: a controlled trial among 1,912,392 Danish adults. *Diabetologia* 2017;**60**(11):2183-91.

Simmons 2017 ADDITION *{published data only}*

Simmons RK, Bruun NH, Witte DR, Borch-Johnsen K, Jørgensen ME, Sandbaek A, et al. Does training of general practitioners for intensive treatment of people with screen-detected diabetes have a spillover effect on mortality and cardiovascular morbidity in 'at risk' individuals with normoglycaemia? Results from the ADDITION-Denmark cluster-randomised controlled trial. *Diabetologia* 2017;**60**(6):1016-21.

Simmons 2017b_ADDITION Denmark *{published data only}*

Simmons RK, Griffin SJ, Lauritzen T, Sandbaek A. Effect of screening for type 2 diabetes on risk of cardiovascular disease and mortality: a controlled trial among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. *Diabetologia* 2017;**60**(11):2192-9.

Skaaby 2018 *{published data only}*

Skaaby T, Jorgensen T, Linneberg A. A randomized general population study of the effects of repeated health checks on incident diabetes. *Endocrine* 2018;**60**(1):122-8.

Sortso 2018 *{published data only}*

Sortso C, Komkova A, Sandbaek A, Griffin SJ, Emneus M, Lauritzen T, et al. Effect of screening for type 2 diabetes on healthcare costs: a register-based study among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. *Diabetologia* 2018;**61**(6):1306-14.

Spijkerman 2003 *{published data only}*

Spijkerman AM, Dekker JM, Nijpels G, Adriaanse MC, Kostense PJ, Ruwaard D, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the Hoorn screening study. *Diabetes Care* 2003;**26**:2604-8.

Su 2017 *{published data only}*

Su XF, Sun L, Liu BL, Tao XJ, Li HQ, Li FF, et al. An intensive diabetes screening and treatment program improves diagnosis, treatment and outcomes of diabetes in patients admitted with cardiac diseases. *Experimental and Clinical Endocrinology & Diabetes* 2017;**125**(3):151-5.

van den Donk 2013 ADDITION *{published data only}*

Van den Donk M, Griffin SJ, Stellato RK, Simmons RK, Sandbaek A, Lauritzen T, et al. Effect of early intensive multifactorial therapy compared with routine care on self-reported health status, general well-being, diabetes-specific quality of life and treatment satisfaction in screen-detected type 2 diabetes mellitus patients (ADDITION-Europe): a cluster-randomised trial. *Diabetologia* 2013;**56**(11):2367-77. [PMID: 23959571]

Villarivera 2012 *{published data only}*

Villarivera C, Wolcott J, Jain A, Zhang Y, Goodman C. Analysis & commentary: the US Preventive Services Task Force should consider a broader evidence base in updating its diabetes screening guidelines. *Health Affairs* 2012;**31**:35-42.

Von Karla 2007 *{published data only}*

Von Karla V, Hewett ML. Type 2 diabetes in children and adolescents: screening, diagnosis, and management. *JAAPA* 2007;**20**:51-4.

References to studies awaiting assessment

Klijs 2012 *{published data only}*

ISRCTN75983009. Population-based randomized controlled trial of screening for type 2 diabetes mellitus in high-risk subjects. www.isrctn.com/ISRCTN75983009 (first received 15 May 2006).

Klijs B, Otto SJ, Heine RJ, van der Graaf Y, Lous JJ, de Koning HJ. Screening for type 2 diabetes in a high-risk population: study design and feasibility of a population-based randomized controlled trial. *BMC Public Health* 2012;**12**:671. [PMID: 22900932]

Willems JI, Otto SJ, Klijs B, de Koning HJ. Screening for type 2 diabetes in a high-risk population: effects of a negative screening test after 4 years follow-up. *Annals of Behavioral Medicine* 2014;**47**(1):102-10. [PMID: 23818042]

Additional references

ADA 2002

American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care* 2002;**25**(Suppl 1):S21-4.

ADA 2003

American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003;**26**(Suppl 1):S5-20.

ADA 2004

American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care* 2004;**27**(Suppl 1):S11-4.

ADA 2008

American Diabetes Association. Standards of medical care - 2008. *Diabetes Care* 2008;**31**:S12-54.

ADA 2010

American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;**33**(Suppl 1):S62-9.

ADA 2014

American Diabetes Association. Diabetes and classification of diabetes mellitus. *Diabetes Care* 2014;**37**(1):S81-90.

Altman 2003

Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;**326**(7382):219. [PMID: 12543843]

Andermann 2008

Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bulletin of the World Health Organization* 2008;**86**(4):317-9.

Bell 2013

Bell ML, McKenzie JE. Designing psycho-oncology randomised trials and cluster randomised trials: variance components and intra-cluster correlation of commonly used psychosocial measures. *Psycho-Oncology* 2013;**22**:1738-47.

Borch-Johnsen 2003

Borch-Johnsen K, Lauritzen T, Glumer C, Sandbaek A. Screening for Type 2 diabetes - should it be now? *Diabetic Medicine* 2003;**20**(3):175-81.

Borenstein 2017a

Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Research Synthesis Methods* 2017;**8**(1):5-18.

Borenstein 2017b

Borenstein M. Prediction intervals. www.meta-analysis.com/prediction (accessed 3 July 2017).

Boutron 2014

Boutron I, Altman DG, Hopewell S, Vera-Badillo F, Tannock I, Ravaud P. Impact of spin in the abstracts of articles reporting results of randomized controlled trials in the field of cancer: the SPIIN randomized controlled trial. *Journal of Clinical Oncology* 2014;**32**(36):4120-6.

Canadian Task Force 2012

Canadian Task Force on Preventive Health Care. Recommendations on screening for type 2 diabetes in adults. *CMAJ* 2012;**184**(15):1687-96.

Carroll 2015

Carroll AE. How useful are screening tests? *JAMA* 2015;**313**(13):1304.

Colagiuri 2002

Colagiuri S, Cull CA, Holman RR. Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?: U.K. Prospective Diabetes Study 61. *Diabetes Care* 2002;**25**(8):1410-7.

Corbett 2014

Corbett MS, Higgins JP, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods* 2014;**5**:79-85.

Deeks 2019

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Diabetes UK 2020

Diabetes UK. Early identification of people with type 2 diabetes; updated: April 2020. www.diabetes.org.uk/professionals/position-statements-reports/type-2-diabetes-prevention-early-identification (accessed prior to 27 May 2020).

Durão 2015

Durão S, Ajumobi O, Kredo T, Naude C, Levitt NS, Steyn K, et al. Evidence insufficient to confirm the value of population screening for diabetes and hypertension in low- and-middle-income settings. *South African Medical Journal* 2015;**105**(2):98-102.

Eborall 2007

Eborall HC, Griffin SJ, Prevost AT, Kinmonth AL, French DP, Sutton S. Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. *BMJ* 2007;**335**(7618):486-93.

Echouffo-Tcheugui 2015

Echouffo-Tcheugui JB, Simmons RK, Prevost AT, Williams KM, Kinmonth AL, Wareham NJ, et al. Long-term effect of population screening for diabetes on cardiovascular morbidity, self-rated health, and health behavior. *Annals of Family Medicine* 2015;**13**(2):149-57.

Expert Committee 1997

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;**20**(7):1183-97.

Griffin 2012

Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbaek A, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 2011;**378**(9786):156-67.

Grimes 2002

Grimes D, Schulz K. Use and abuses of screening tests. *Lancet* 2002;**359**(9309):881-4.

Harris 1992

Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 1992;**15**(7):815-9.

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539-58.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557-60.

Higgins 2019a

Higgins JP, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Higgins 2019b

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**:13. [DOI: 10.1186/1471-2288-5-13]

Hróbjartsson 2013

Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *Canadian Medical Association Journal* 2013;**185**(4):E201-11.

IDF 2012

Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation, 2012.

IDF 2019

International Diabetes Federation. IDF Diabetes Atlas, ninth edition 2019. Available at: https://www.diabetesatlas.org 2019.

International Expert Committee 2009

International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;**32**:1327-34.

Inzucchi 2012

Inzucchi SE. Clinical practice. Diagnosis of diabetes. *New England Journal of Medicine* 2012;**367**(6):542-50.

Jones 2015

Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. *BMC Medicine* 2015;**13**:282. [DOI: 10.1186/s12916-015-0520-3]

Kirkham 2010

Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365. [DOI: 10.1136/bmj.c365]

Lauritzen 2000

Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with type 2 diabetes detected by screening. *International Journal of Obesity and Related Metabolic Disorders* 2000;**24 Suppl 3**:S6-11. [PMID: 11063279]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLOS Medicine/Public Library of Science* 2009;**6**:e1000100. [DOI: 10.1371/journal.pmed.1000100]

Mathieu 2009

Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA* 2009;**302**:977-84.

Meader 2014

Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility

of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**3**:82.

Peer 2014

Peer N, Kengne AP, Motala A, Mbanya JC. Diabetes in the Africa region: an update. *Diabetes Research and Clinical Practice* 2014;**103**(2):197-205.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Riley 2011

Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.

Rutten 2006

Rutten GE, de Grauw WJ, Nijpels G, Goudswaard AN, Uitewaal PJ, van der Does FE, et al. Dutch College of General Practitioners' guidelines on type 2 diabetes mellitus (second revision). *Huisarts en Wetenschap* 2006;**49**:137-52.

Sandbaek 2008

Sandbaek A, Griffin SJ, Rutten G, Davies M, Stolk R, Khunti K, et al. Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia* 2008;**51**(7):1127-34.

Saquib 2015

Saquib N, Saquib J, Ioannidis JP. Does screening for disease save lives in asymptomatic adults? Systematic review of meta-analyses and randomized trials. *International Journal of Epidemiology* 2015;**44**(1):264-77.

Schünemann 2019

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the confidence in or quality of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Selph 2015

Selph S, Dana T, Blazina I, Bougatsos C, Patel H, Chou R. Screening for type 2 diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2015;**162**:765-76.

Sherifali 2013

Sherifali D, Fitzpatrick-Lewis D, Peirson L, Ciliska D, Coyle D. Screening for type 2 diabetes in adults: an updated systematic review. *Open Diabetes Journal* 2013;**6**:1-13.

Standing committee on screening 2018

Standing Committee on Screening. Population based screening framework; updated August 2018. www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/population-based-screening-framework.

Sterne 2017

Sterne JA, Egger M, Moher D, Boutron I (editors). Chapter 10: Addressing reporting biases. In: Higgins JP, Churchill R, Chandler J, Cumpston MS (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Waugh 2007

Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, et al. Screening for type 2 diabetes: literature review and economic modelling. *Health Technology Assessment* 2007;**11**(17):1-125.

Waugh 2013

Waugh NR, Shyangdan D, Taylor-Phillips S, Suri G, Hall B. Screening for type 2 diabetes: a short report for the National Screening Committee. *Health Technology Assessment* 2013;**17**(35):1-90. [DOI: 10.3310/hta17350]

WHO 1985

WHO Study Group on Diabetes Mellitus & World Health Organization. Diabetes mellitus: report of a WHO study group [meeting held in Geneva from 11 to 16 February 1985]. World Health Organization technical report series ; no. 727. apps.who.int/iris/handle/10665/39592.

WHO 1999

World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. apps.who.int/iris/handle/10665/66040.

WHO 2003

World Health Organization. Screening for type 2 diabetes. Report of a WHO and IDF meeting. who.int/diabetes/publications/screening2003/en/.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**(7644):601-5.

References to other published versions of this review

Klein Woolthuis 2005

Klein Woolthuis EP, De Grauw WJC, Van de Laar FA, Akkermans RP. Screening for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD005266]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Simmons 2012

Study characteristics	
Methods	**Study design**: pragmatic parallel-group, unbalanced, cluster-randomised trial; randomisation ratio: 1:6 randomisation of practices
Participants	**Inclusion criteria**: individuals eligible for an invitation for screening were men and women registered with 1 of the participating general practices, aged 40 to 69 years, not known to have diabetes and with a diabetes risk score of > 0.17 (corresponding to the top 25% of the population distribution) **Exclusion criteria**: pregnancy, lactation, an illness with a likely prognosis of less than 1 year, or a psychiatric illness likely to limit study involvement or invalidate informed consent **Diagnostic criteria**: a stepwise programme was used for the diagnosis of diabetes. This included a random capillary blood glucose and HbA1c tests, a fasting capillary blood glucose test, and confirmation on OGTT
Interventions	Screening for diabetes compared to not screening for diabetes in high-risk individuals. Those diagnosed with diabetes after screening (OGTT) received either intensive multifactorial treatment (IT) or routine care (RC) according to which arm the practice they attended had been randomised to. **Number of study centres**: 32 general practices participated and were randomised to a screening intervention group (N = 27; 13 to screening and RC and 14 to screening and IT) or to a no-screening control group (N = 5)
Outcomes	Proportion of people who responded to the invitation for screening diagnosed with diabetes. • All-cause mortality • Cardiovascular, cancer, and diabetes-related mortality • Prevalence of cardiovascular events (self-reported) • Health-related quality of life (EQ-5D and visual analogue scores) • Mental health: state anxiety (Spielberger state anxiety inventory), anxiety and depression (hospital anxiety and depression scale), worry about diabetes
Study details	**Study ID**: ISRCTN86769081
Publication details	**Language of publication**: English **Funding:** the study was supported by the Wellcome Trust, the Medical Research Council, and National Health Service R&D support funding. Some authors were members of the National Institute for Health Research (NIHR) School for Primary Care Research. The General Practice and Primary Care Research Unit is supported by NIHR research funds. SJG receives support from the Department of Health NIHR Programme Grant funding scheme (RP-PG-0606-1259). **Publication status:** peer-reviewed journal
Stated aim of study	**Quote:** "To evaluate the effectiveness and cost effectiveness of (i) a stepwise screening strategy for type 2 diabetes; and (ii) intensive multifactorial treatment for people with screen-detected diabetes in primary care"
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Simmons 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	**Quote:** "Randomisation was undertaken by a statistician using the method of minimisation. In the first stage of randomisation, 33 recruited practices were allocated (1:3:3) to one of three groups: no screening (control; five practices), screening followed by intensive treatment of patients with screen-detected diabetes (IT; 15 practices), and screening plus routine care of patients with screen-detected diabetes (RC; 13 practices). These practices are included in the main trial analysis of screening versus control presented here. One of the 28 screening practices dropped out before screening commenced because of logistical difficulties with identification of people at high risk. The need to achieve the required sample size of patients with screen-detected diabetes for the treatment trial warranted the uneven randomisation ratio with a disproportionate number of screening practices and a second stage of randomisation. 27 practices were subsequently randomly assigned (1:1) to IT (n=14) and RC (n=13). The final group allocation after the two stages of randomisation included 28 practices to IT, 27 to RC, and five to control (no screening). A further six randomised practices (two IT and four RC) dropped out after recruitment, but before screening commenced because of other commitments or unforeseen difficulties in setting up the practice-based screening programme. Results from all practices included in the final group allocation are also presented in a parallel cohort analysis. This design has the advantage of increasing the sample size for the comparison of screened versus control practices, but increases the possibility of confounding and selection bias" **Comment:** randomisation was done centrally; however, it is unknown how and which participants were chosen in the practices to participate in the screening or no-screening intervention
Allocation concealment (selection bias)	Unclear risk	**Comment:** randomisation was done centrally; however, it is unknown how and which participants were chosen in the practices to participate in the screening or no-screening intervention
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	**Comment:** lack of blinding unlikely to have influenced this outcome
Blinding of participants and personnel (performance bias) diabetes-related mortality	Low risk	**Comment:** lack of blinding unlikely to have influenced this outcome
Blinding of participants and personnel (performance bias) diabetes-related morbidity	High risk	**Quote:** "The questionnaire elicited patients' experience of cardiovascular disease events" **Comment:** lack of blinding likely to have influenced this outcome
Blinding of participants and personnel (performance bias) health-related quality of life	High risk	**Comment:** lack of blinding likely to have influenced this outcome
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	**Quote:** "All eligible participants were flagged for mortality surveillance by the England and Wales Office of National Statistics, with unique NHS patient numbers. This classification was independently done by an assessor masked to randomisation group status. 50% of the deaths were classified by a second assessor with 98% agreement. Consensus was reached by discussion."

Simmons 2012 *(Continued)*

		Quote: "The investigators assessing outcomes and analysing data were masked to group assignment"
Blinding of outcome assessment (detection bias) diabetes-related mortality	Low risk	**Quote:** "All eligible participants were flagged for mortality surveillance by the England and Wales Office of National Statistics, with unique NHS patient numbers. This classification was independently done by an assessor masked to randomisation group status. 50% of the deaths were classified by a second assessor with 98% agreement. Consensus was reached by discussion." **Quote:** "The investigators assessing outcomes and analysing data were masked to group assignment"
Blinding of outcome assessment (detection bias) diabetes-related morbidity	High risk	**Quote:** "The questionnaire elicited patients' experience of cardiovascular disease events" **Comment:** outcomes of heart attack and stroke are self-reported without clinical confirmation
Blinding of outcome assessment (detection bias) health-related quality of life	High risk	**Comment:** lack of blinding likely to have influenced this outcome
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	**Comment:** all eligible participants were flagged for mortality surveillance by the England and Wales Office of National Statistics, with unique NHS patient numbers, and there was only 1% loss to follow-up. No clusters were lost during the study.
Incomplete outcome data (attrition bias) diabetes-related mortality	Low risk	**Comment:** all eligible participants were flagged for mortality surveillance by the England and Wales Office of National Statistics, with unique NHS patient numbers, and there was only 1% loss to follow-up. No clusters were lost during the study.
Incomplete outcome data (attrition bias) diabetes-related morbidity	High risk	**Quote:** "The response rate was 62% in the screening group and 53% in the control group."; "Responders to the questionnaire were more likely to be older, to be female, to have been prescribed antihypertensive medication to have a low body mass index (BMI), and to have exhibited a higher risk of undiagnosed diabetes at baseline than non-responder"
Incomplete outcome data (attrition bias) health-related quality of life	High risk	**Quote:** "The response rate was 62% in the screening group and 53% in the control group."; "Responders to the questionnaire were more likely to be older, to be female, to have been prescribed antihypertensive medication to have a low body mass index (BMI), and to have exhibited a higher risk of undiagnosed diabetes at baseline than non-responder"
Selective reporting (reporting bias)	Low risk	**Comment:** all outcomes and methods described as prespecified in the protocol
Other bias	Low risk	Cluster RCT (recruitment bias): low; study accounted for clustering of practices. Randomisation was done at the practice and not at the level of the individual. Individuals already belonged to specific practices. Cluster RCT (baseline imbalance): low; there were no differences at the cluster and individual levels to clinically impact on outcomes. Cluster RCT (loss of clusters): low; no clusters were lost during the study. Cluster RCT (incorrect analysis): study accounted for clustering of practices in the analysis.

HbA1c: glycosylated haemoglobin A1c; **OGTT**: oral glucose tolerance test; **RCT**: randomised controlled trial.
Note: where the judgement is 'unclear' and the description is blank, the study did not report that particular outcome.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acosta 2018	Intervention not eligible: presents baseline characteristics of a lifestyle project for diabetes prevention (DEMOJUAN project)
ACTRN12611000518965	Intervention not eligible - study of intervention to improve screening and management of type 2 diabetes by Aboriginal Community Control Health Organisations (ACCHOs)
ACTRN12616001240437	Study design not eligible - comparison of different screening tools rather than screening vs no screening
ADDITION-Leicester 2015	Intervention not eligible
Black 2014	Study design not eligible - study of a subset of participants of a randomised trial with complete data at follow-up
Black 2015	Study design ineligible - prospective cohort study
Charles 2011 ADDITION	Intervention not eligible - study of treating patients with screen-detected diabetes on neuropathy and peripheral arterial disease
Charles 2013 ADDITION	Intervention not eligible - study of treating patients with screen-detected diabetes on cardiac autonomic neuropathy
Charles 2017 ADDITION	Intervention not eligible - study of training of general practitioners in intensive treatment of people with screen-detected diabetes
ChiCTR1800015274	Ineligible study population - pregnant women
ChiCTR1800017260	Ineligible study design - cohort study
CTRI/2016/09/007323	Ineligible study design - cohort study
CTRI/2017/10/010199	Ineligible participants - patients with tuberculosis
CTRI/2018/08/015536	Ineligible study design - cross-sectional study
CTRI/2018/08/015568	Ineligible study population - individuals with diabetes
CTRI/2018/12/016532	Ineligible study design - uncontrolled cohort study
Dalsgaard 2010 ADDITION Denmark	Ineligible intervention - costs associated with different screening approaches
Dalsgaard 2014 ADDITION	Intervention not eligible - study of intensive treatment vs routine care in patients with screen-detected diabetes
den Ouden 2015 ADDITION	Ineligible intervention - study of intensive treatment in patients with screen-detected diabetes
DRKS00009837	Ineligible study design - uncontrolled study
Dunkley 2017	Ineligible study design - cohort study
Eborall 2007 ADDITION	Study design not eligible - comparative study embedded in an RCT

Study	Reason for exclusion
Griffin 2011 ADDITION	Intervention not eligible - study of intensive treatment vs routine care in patients with screen-detected diabetes
Harris 2003	Ineligible study design - systematic review
Hellgren 2015	Ineligible study design - prospective epidemiological study
Herman 2015	Study design not eligible - not an RCT
ISRCTN21333761	Ineligible intervention - study about personalised clinical visits
ISRCTN57962668	Ineligible study design - cross-sectional study
Johansen 2012 ADDITION	Intervention not eligible - study of intensive treatment vs routine care in patients with screen-detected diabetes
Juul 2009 ADDITION	Intervention not eligible - study of adherence to treatment guidelines for patients with screen-detected diabetes
Kenealy 2007	Study design not eligible - not an RCT
Kolaczynski 2000	Study design not eligible - not an RCT
Kullgren 2017	Ineligible patient population
Kumar 2015	Ineligible intervention - study about mobile reminders for people to come in for additional tests
Kuznetsov 2015 ADDITION	Intervention not eligible - study comparing perceptions of care amongst those with screen-detected diabetes in intensive treatment vs routine care
Lau 2016	Ineligible study design - the population with diabetes was discarded at the beginning of the study, thus removing the randomised aspect of the study
Lauritzen 2000 ADDITION	Intervention not eligible - study of cost-effectiveness of intensive multifactorial intervention for people with screen-detected diabetes
Lauritzen 2011 ADDITION	Study design not eligible - cohort analysis embedded in an RCT
Law 2018	Ineligible intervention - all participants were screened, and study assessed immediate vs delayed feedback on screening
Maindal 2013 ADDITION	Intervention not eligible - study of health education vs control in patients with screen-detected diabetes
Monti 2012	Study design not eligible - not an RCT
NCT00007696	Study design not eligible - not an RCT
NCT00042042	Study design not eligible - not an RCT
NCT00253240	Study design not eligible - not an RCT
NCT00377117	Study design not eligible - not an RCT
NCT01591525	Study design not eligible - not an RCT

Study	Reason for exclusion
NCT02223793	Intervention not eligible - study of behavioural intervention after cardiovascular risk screening, not of screening vs no screening
NCT02418637	Study design not eligible - not an RCT
NCT02513277	Study design not eligible - not an RCT
NCT02750527	Study design not eligible - not an RCT
NCT03254979	Patient population not eligible - includes patients with diabetes
NCT03395509	Study design not eligible - not an RCT
Park 2008	Intervention not eligible - follow-up shorter than 3 months
Raikou 2003	Study design not eligible - not an RCT
Rasmussen 2016	Study design not eligible - not an RCT
Reid 1974	Study design not eligible - not an RCT
Rubak 2009 ADDITION	Intervention not eligible - study of training general practitioners in motivational interviewing for people with type 2 diabetes
Scherstén 1966	Ineligible study design - no control group
Simmons 2011	Study design not eligible - not an RCT
Simmons 2012b ADDITION	Intervention not eligible - study of intensive multifactorial treatment in people with screen-detected diabetes
Simmons 2014 ADDITION	Intervention not eligible - study of intensive treatment vs routine care in patients with screen-detected diabetes
Simmons 2017 ADDITION	Intervention not eligible - study of training of general practitioners in intensive treatment of people with screen-detected diabetes
Simmons 2017a_ADDITION Denmark	Study design not eligible - not a randomised trial
Simmons 2017b_ADDITION Denmark	Study design not eligible - not a randomised trial
Skaaby 2018	Ineligible intervention - no screening for diabetes carried out with the health checks
Sortso 2018	Study design not eligible - not a randomised trial
Spijkerman 2003	Study design not eligible - not an RCT
Su 2017	Ineligible patient population
van den Donk 2013 ADDITION	Intervention not eligible - study of intensive treatment vs routine care in patients with screen-detected diabetes
Villarivera 2012	Study design not eligible - not an RCT

Study	Reason for exclusion
Von Karla 2007	Study design not eligible - not an RCT

RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Klijs 2012

Methods	**Type of study:** parallel RCT
Participants	**Inclusion criteria**: inhabitants of 2 Dutch municipalities, males and females aged 40 to 74, absence of pre-existing diabetes, indication of abdominal obesity, individuals in the control and screening groups were eligible for the current study if they had completed the questions pertaining to general health, smoking behaviour, and symptom risk for diabetes in the 2006 questionnaire and had a negative screening test result in 2006 if in the screening group. The age- and sex-matched control group had no screening test. **Exclusion criteria**: a diagnosis of diabetes or IFG **Diagnostic criteria**: fasting plasma glucose (FPG) level ≥ 7.0 mmol/L diagnosed diabetes, and FPG level of 6.1 to 6.9 mmol/L diagnosed IFG.
Interventions	A negative screening test for diabetes
Outcomes	BMI, waist circumference, diabetes risk perception, personal control, worry, optimistic bias
Reason for awaiting classification	Klijs 2012 is a protocol. The study is complete according to the record in the trials registry, but there are no published reports. We contacted the author for information regarding the study's findings but as of yet have received no reply.
Stated aim of study	Aim not reported. Study hypothesis: "Systematic screening for type 2 diabetes in high-risk obese subjects, identified from the general population, can significantly reduce the diabetes-related cardiovascular morbidity and mortality by at least 25% compared with not offering a screening program."
Study details	**Language of publication**: English **Funding:** ZonMW (Zorgonderzoek Nederland - Medische Wetenschappen) **Publication status:** peer-reviewed journal **Trial identifier:** ISRCTN75983009
Notes	Willems 2014 is a substudy of Klijs 2012; it includes some of the population in the main RCT but does not assess a relevant comparison for this review and therefore has not been included.

— denotes not reported
ADDITION: Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; **BMI**: body mass index; **FPG**: fasting plasma glucose; **IFG**: impaired fasting glucose; **RCT**: randomised controlled trial.

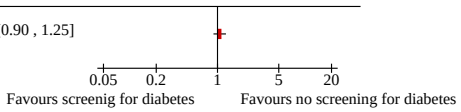
DATA AND ANALYSES

Comparison 1. Screening for diabetes versus no screening for diabetes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
1.2 Diabetes-related mortality	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
1.3 Cardiovascular mortality	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
1.4 Cancer mortality	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected

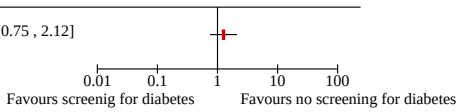
Analysis 1.1. Comparison 1: Screening for diabetes versus no screening for diabetes, Outcome 1: All-cause mortality

Study or Subgroup	log[Other]	SE	Screening for diabetes Total	No screening for diabetes Total	Other IV, Fixed, 95% CI	Other IV, Fixed, 95% CI
Simmons 2012	0.0583	0.0835	16047	4137	1.06 [0.90 , 1.25]	



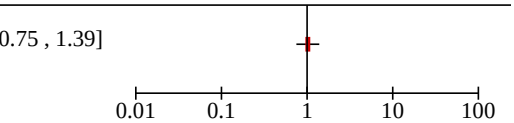
Analysis 1.2. Comparison 1: Screening for diabetes versus no screening for diabetes, Outcome 2: Diabetes-related mortality

Study or Subgroup	log[Other]	SE	Screening for diabetes Total	No screening for diabetes Total	Other IV, Fixed, 95% CI	Other IV, Fixed, 95% CI
Simmons 2012	0.2311	0.2647	16047	4137	1.26 [0.75 , 2.12]	



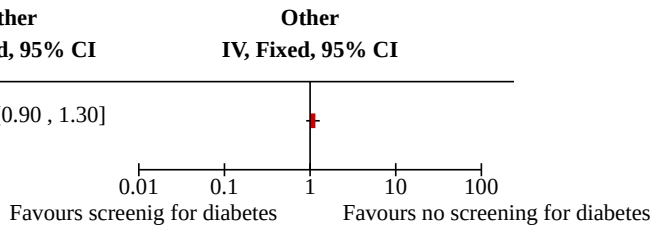
Analysis 1.3. Comparison 1: Screening for diabetes versus no screening for diabetes, Outcome 3: Cardiovascular mortality

Study or Subgroup	log[Other]	SE	Other IV, Fixed, 95% CI	Other IV, Fixed, 95% CI
Simmons 2012	0.0198	0.1569	1.02 [0.75 , 1.39]	



Analysis 1.4. Comparison 1: Screening for diabetes versus no screening for diabetes, Outcome 4: Cancer mortality

Study or Subgroup	log[Other]	SE	Other IV, Fixed, 95% CI
Simmons 2012	0.077	0.093	1.08 [0.90 , 1.30]



ADDITIONAL TABLES

Table 1. Overview of study populations

Study ID (study design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (N)	Randomised (N)	Analysed (primary outcome) (N)	Finishing trial (N)	Randomised finishing trial (%)	Follow-up
Simmons 2012 (cluster-RCT)	I: individuals at high risk for diabetes invited for screening	"The study sample size was originally estimated to quantify the effectiveness of intensive treatment in screen-detected patients via detection of a 20% relative difference in the UK Prospective Diabetes Study (UKPDS) modelled 10-year risk of cardiovascular disease between participants with screen-detected diabetes in the IT and RC groups"	138 practices/63 practices	27 practices (14 to IT, 13 to RC) 16,047 eligible participants (mean 594 (SD 340) per practice) 15,089 participants invited for screening 11,737 participants attended screening	16,047[a]	—	—	Median duration of intervention: 9.6 years (IQR 8.9 to 9.9)
	C: individuals at high risk for diabetes not invited for screening			5 practices 4137 eligible participants (mean 827 (SD 228) per practice)	4137	—	—	
	Total:			**20,184**				
Grand total	**All interventions**			**11,737** [a]		—		
	All comparators			**4137**		—		
	All interventions and comparators			**15,874** [a]		—		

— denotes not reported

[a]Numbers analysed by study authors ("Analyses were done on an intention-to-screen basis at the population level. All eligible high-risk individuals were considered in analyses irrespective of their participation in the screening programme (this population included non-attenders and high-risk patients deemed unfit for screening by their general practitioner")

C: comparator; **I**: intervention; **IQR**: interquartile range; **IT**: screening followed by intensive treatment of participants with screen-detected diabetes; **RC**: screening followed by routine care according to national guidelines of participants with screen-detected diabetes; **RCT**: randomised controlled trial; **SD**: standard deviation.

APPENDICES

Appendix 1. Diagnostic criteria for diabetes as defined by expert committees

Expert committees	Criteria			
	Fasting plasma glucose[a]	2-hour plasma glucose[b]	Random plasma glucose	HbA1c
World Health Organization (WHO)				
1985 (WHO 1985)	≥ 7.8 mmol/L (≥ 140 mg/dL)	≥ 11.1 mmol/L (≥ 200 mg/dL)	NA	NA
1998 (WHO 1999)	≥ 7.0 mmol/L (≥ 126 mg/dL)	≥ 11.1 mmol/L (≥ 200 mg/dL)	NA	NA
American Diabetes Association (ADA)				
1997 (Expert Committee 1997)	≥ 7.0 mmol/L (≥ 126 mg/dL)	Not recommended	NA	NA
2003 (ADA 2003)	≥ 7.0 mmol/L (≥ 126 mg/dL)	≥ 11.1 mmol/L (≥ 200 mg/dL)	Symptoms of diabetes + ≥ 11.1 mmol/L (≥ 200 mg/dL)	NA
2010 (ADA 2010)	≥ 7.0 mmol/L (≥ 126 mg/dL	≥ 11.1 mmol/L (≥ 200 mg/dL)	≥ 11.1 mmol/L (≥ 200 mg/dL	≥ 6.5% (≥ 48 mmol/mol)

[a]Following an overnight fast of ≥ 8 hours.
[b]During an oral glucose tolerance test.

HbA1c: glycosylated haemoglobin A1c; **NA**: not applicable.

Appendix 2. Search strategies

CENTRAL (CRSO)
1. MESH DESCRIPTOR Mass Screening
2. screening?:TI,AB,KY
3. (screened or detect or detected or detection):TI
4. #1 OR #2 OR #3
5. MESH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES
6. (MODY OR NIDDM OR T2DM OR T2D):TI,AB,KY
7. diabet*:TI,AB
8. #5 OR #6 OR #7
9. MESH DESCRIPTOR Diabetes Insipidus EXPLODE ALL TREES
10. ("diabet* insipidus"):TI,AB,KY

(Continued)

11. #9 OR #10

12. #8 NOT #11

13. #4 AND #12

14. NCT*:AU *[filters for ClinicalTrials.gov records]*

15. trialsearch:SO *[filters for WHO ICTRP records]*

16. #14 OR #15

17. #13 NOT #16

MEDLINE (Ovid SP)

1. exp Mass Screening/

2. (screening?).tw.

3. (screened or detect or detected or detection).ti.

4. or/1-3

5. exp Diabetes Mellitus, Type 2/

6. (MODY or NIDDM or T2DM or T2D).tw.

7. (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.

8. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.

9. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).tw.

10. or/5-9

11. exp Diabetes Insipidus/

12. diabet* insipidus.tw.

13. 11 or 12

14. 10 not 13

15. 4 and 14

[16-26: Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

16. randomized controlled trial.pt.

17. controlled clinical trial.pt.

18. randomi?ed.ab.

19. placebo.ab.

20. drug therapy.fs.

21. randomly.ab.

22. trial.ab.

23. groups.ab.

24. or/16-23

25. exp animals/ not humans/

(Continued)

26. 24 not 25

27. 15 and 26

LILACS (IAHx)

(MH:"Mass Screening" OR screen$ OR cheq$ OR criba$ OR detec$ OR rastr$ OR triag$) AND (MH:"Diabetes Mellitus, Type 2" OR diabet$)

+ Filter "Controlled Clinical Trial"

ICTRP Search Portal (Standard search)

screening* AND diabet*

ClinicalTrials.gov (Advanced search)

Conditions: diabetes OR diabetic

Interventions: screening OR screenings OR screened OR screen OR detection OR detecting OR detected

Study type: Interventional Studies

Appendix 3. 'Risk of bias' assessment

'Risk of bias' domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: study authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the study. We considered the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, Internet-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We also evaluated study baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014).

(Continued)

Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between studies judged as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies judged as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We reclassified judgements of unclear, low, or high risk of selection bias as specified in Appendix 4.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the study)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the study does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of study participants and key personnel attempted, but it is likely that the blinding could have been broken, and the outcome is likely to have been influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the study did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding; blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to have been influenced by lack of blinding.

Incomplete outcome data (attrition bias due to quantity, nature, or handling of incomplete outcome data)

For each included study or each outcome, or both, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the study reported attrition and exclusions, and reported the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also noted if the study reported the reasons for attrition or exclusion, and whether missing data were balanced across groups or were related to outcomes. We considered the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between study arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) amongst missing outcomes is not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle the missing data were likely to induce bias; the study did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either an imbalance in the numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) amongst missing outcomes is enough to induce clinically relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We assessed outcome reporting bias by integrating the results of Appendix 9 'Matrix of study endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of Appendix 10 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting.

(Continued)

- Low risk of bias: the study protocol was available, and all the study's prespecified (primary and secondary) outcomes that were of interest to the review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that we could not enter them into a meta-analysis; the study report failed to include results for a key outcome that we would have expected to have been reported for such a study (ORBIT classification).

Other bias

- Low risk of bias: the study appears to be free from other sources of bias.
- Unclear risk of bias: information was insufficient to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the study had a potential source of bias related to the specific study design used; the study was claimed to be fraudulent; or the study had some other serious problem.

Appendix 4. Selection bias decisions

Selection bias decisions for studies reporting unadjusted analyses - comparison of results obtained using method details alone with results using method details and study baseline information[a]

Reported randomisation and allocation concealment methods	'Risk of bias' judgement using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	**High risk**
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	**Unclear risk[c]**
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables[b]	Low risk
		No baseline details	**Unclear risk**
Sequence is not truly random, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	**Low risk**

(Continued)

	Limited baseline details, showing balance in some important prognostic variables[b]	**Unclear risk**
	No baseline details	High risk

[a]Taken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.
[b]Details for the remaining important prognostic variables not reported.
[c]Imbalance identified that appears likely to be due to chance.

Appendix 5. Description of interventions and comparators

Item	Study ID: Simmons 2012
Study author	Simmons 2012
Brief name	ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) trial
Recipient	20,184 participants from 33 general practices in Eastern England, at high risk for diabetes
Why	The high proportion of undiagnosed diabetes, the substantial burden of complications at clinical diagnosis, and the long latent phase of the disease are arguments in favour of screening for diabetes.

What (materials)	• Validated diabetes risk score to identify patients at high risk (score > 0.17) for diabetes
	• Standardised quality of life questionnaire:
	  ◦ EuroQoL (EQ-5D)
	  ◦ 36-item Short Form Health Survey (SF-36)
	  ◦ 8-item Short Form Health Survey (SF-8)
	• Diabetes-related quality of life: Audit of Diabetes-Dependent Quality of Life (ADDQoL)
	• Adverse events questionnaire
	• Spiegelberger short form state anxiety inventory

What (procedures)	Testing of random or fasting capillary blood glucose in high-risk patients involved a finger prick test. Oral glucose tolerance test (OGTT) involved an overnight fast of about 10 hours followed by drawing a venous blood sample, the administration of 75 g of anhydrous glucose in 250 mL of water, and another blood sample taken 120 minutes later.
Who provided	"In the participating practices, a 'set-up' visit was undertaken to deliver practice study manuals, to provide the software developed to assist with monitoring the progress of the screening programme and recording of blood glucose test results, and to train the staff in logistical and technical aspects of screening. Further visits were arranged for practices allocated to screening followed by intensive treatment to provide the materials and training to enable them to deliver the intervention." (Echouffo-Tcheugui 2009, linked to Simmons 2012)
How (mode of delivery; individual or group)	"In practices in the RC and IT groups, general practitioners wrote to all high-risk patients, enclosing a study information sheet, and inviting them to attend the practice for random capillary blood glucose (RBG) and capillary glycosylated haemoglobin (HbA1c) tests, after initial consent had been obtained." "Patients were advised to telephone the surgery and arrange an alternative appointment if

(Continued)

	the original was inconvenient. One reminder letter was sent to non-attendees." (Echouffo-Tcheugui 2009, linked to Simmons 2012). Screenings were provided on an individual basis.
Where	OGTT was conducted at 1 of 4 outpatient facilities. Random and fasting blood glucose testing were undertaken at the general practitioner practices on different days.
When and how much	Each glucose test was done once. The number of tests done per patient depended on the results of each test. Testing was conducted on different days at the patient's convenience.
Tailoring	"Participants with an RBG of ≥ 11.1 mmol/L were invited for a standard 75 g oral glucose tolerance test (OGTT) at one of four outpatient facilities. Those with an RBG of 5.5–11.0 mmol/L were invited to return to the practice for a fasting capillary blood glucose (FBG) test. Those with an FBG of ≥ 6.1 mmol/L, or an FBG of 5.5–6.0 mmol/L together with an HbA1c of ≥ 6.1%, were invited for an OGTT. The RBG, FBG and OGTT were conducted on different days. Participants with an FBG of 5.5–6.0 mmol/L and an HbA1c of ≥ 6.1% who had a positive OGTT underwent a second confirmatory OGTT on a different day." (Echouffo-Tcheugui 2009, linked to Simmons 2012)
Modification of intervention throughout the trial	Not applicable for diabetes screening
Strategies to improve or maintain intervention fidelity	Not applicable for diabetes screening. "The invitation list for screening was defined at the outset of the study; practices were asked to invite only the patients on the list that we provided." "Practices were eligible to take part if they could provide data for calculation of the risk score for at least 70% of their patients" (Simmons 2012)
Extent of intervention fidelity	Not tested

EQ-5D: EuroQol measure of health outcome; **HbA1c**: glycosylated haemoglobin A1c; **IT**: intensive treatment; **OGTT**: oral glucose tolerance test; **RBG**: random capillary blood glucose; **RC**: routine care.

Appendix 6. Baseline characteristics (I)

Study ID	Intervention(s) and comparator(s)	Duration of intervention (follow-up)	Description of participants	Diagnostic criteria for type 2 diabetes	Study period (year to year)	Country	Setting	Ethnic groups (%)
Simmons 2012	I: High-risk individuals invited for screening for diabetes	Median 9.6 years follow-up	People registered with 1 of the participating general practices, aged 40 to 69 years, not known to have diabetes, and with a diabetes risk score[a] of > 0.17	75 g OGTT (1999 WHO criteria)	November 2001 to November 2011	United Kingdom	General practices in Eastern England	—
	C: High-risk individuals not invited for screening for diabetes							—

—: denotes not reported

C: comparator; **I**: intervention; **OGTT**: oral glucose tolerance test; **WHO**: World Health Organization.

[a]The score consisted of age, gender, body mass index, steroid and antihypertensive medication, family and smoking history.

Appendix 7. Baseline characteristics (II)

Study ID	Intervention(s) and comparator(s)	Sex (female %)	Age (mean years (SD))	HbA1c (mean % (SD))	FBG (mean mg/dL (SD))	BMI (mean kg/m² (SD))	Co-medications/Co-interventions (% of participants)	Comorbidities (% of participants)
Simmons 2012	I: High-risk individuals invited for screening for diabetes	36	58.2 (7.7)	—	—	30.5 (4.6)	Antihypertensive medication: 45.9 Prescribed steroids: 5.4	—
	C: High-risk individuals not invited for screening for diabetes	36	57.9 (7.8)	—	—	30.6 (4.6)	Antihypertensive medication: 44.8 Prescribed steroids: 3.7	—

—: denotes not reported

BMI: body mass index; **C**: comparator; **FBG**: fasting blood glucose; **HbA1c**: glycosylated haemoglobin A1c; **I**: intervention; **SD**: standard deviation.

Appendix 8. Study endpoints and timing of outcome measurement

Study ID	Primary and secondary outcomes of this review	Timing of outcome measurement
Simmons 2012	All-cause mortality	10 years
	Diabetes-related mortality	10 years
	Diabetes-related morbidity	7 years
	Incidence of type 2 diabetes	—
	Health-related quality of life	7 years
	Adverse events	7 years
	Socioeconomic effects	—

—: denotes not reported

Appendix 9. Matrix of study endpoints (publications and trial documents)

Study ID	Endpoints
Simmons 2012	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,b]
	Primary outcome measure(s): **Source 1:** NCT00237549 (ISRCTN86769081) Cardiovascular mortality, myocardial infarction (non-fatal), stroke (non-fatal), revascularisation (operating procedures), amputations, non-traumatic **Source 2** (published protocol): Echouffo-Tcheugui 2009 under Simmons 2012 *"At one year follow-up* the principle outcome is modelled 10-year risk of cardiovascular events derived using the UKPDS risk engine" "*At five-year follow-up*, the primary endpoint is a composite of cardiovascular mortality and morbidity (non-fatal myocardial infarction, non-fatal stroke, non-traumatic amputations and revascularizations)" **Secondary outcome measure**(s): **Source 1:** NCT00237549 (ISRCTN86769081) All-cause mortality, development of renal impairment, progression of retinopathy, health economy, patient and health service costs and gains, perceived health, SF-36, ADDQol, neuropathy, periphery and autonomy **Source 2** (published protocol): Echouffo-Tcheugui 2009 under Simmons 2012 All-cause mortality, development or progression of renal impairment, peripheral neuropathy, blindness, reduced visual acuity, macular oedema, retinopathy; health status, health utility, quality of life, anxiety, well-being, treatment satisfaction, health service costs (number of visits to general

(Continued)

practitioners and hospital doctors for outpatient clinics, hospital admissions and prescribed medications)

Other outcome measure(s) (intermediate endpoints)

Source 1: NCT00237549 (ISRCTN86769081)

Source 2 (published protocol): Echouffo-Tcheugui 2009 under Simmons 2012

Self-reported smoking status, diet, physical activity behaviour and medication adherence, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, blood pressure, modelled 10-year cardiovascular risk (at 5-year follow-up), self-reported hypoglycaemic episodes, microalbuminuria, body mass index, and plasma vitamin C

Trial results available in trial register: yes

Endpoints quoted in publication(s)[b,c]

Primary outcome measure(s): all-cause mortality

Secondary outcome measure(s): death from cardiovascular disease, cancers, and other causes; diabetes-related death, health-related quality of life, mental health

Other outcome measure(s): other outcomes listed in the ADDITION trial registry entry were published in various ADDITION papers; we excluded these from our review as they did not address the question of screening versus no screening, but rather the question of intensive versus routine care for screen-detected diabetes

Endpoints quoted in abstract of publication(s)[b,c]

Primary outcome measure(s): all-cause mortality

Secondary outcome measure(s): cardiovascular mortality, cancer mortality, diabetes-related mortality

Other outcome measure(s): —

—: denotes not reported
[a]Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).
[b]Primary and secondary outcomes refer to verbatim specifications in publication/records. Unspecified outcome measures refer to all outcomes not described as primary or secondary outcome measures.

[c]Publication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary trial).

ADDITION: Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; **ADDQol**: Audit of Diabetes-Dependent Quality of Life; **EMA**: European Medicines Agency; **FDA**: US Food and Drug Administration; **HbA1c**: glycosylated haemoglobin A1c; **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **SF-36:** 36-item Short Form Health Survey; **UKPDS**: UK Prospective Diabetes Study.

Appendix 10. High risk of outcome reporting bias according to Outcome Reporting Bias In Trials (ORBIT) classification

Study ID	Outcome	High risk of bias (category A)[a]	High risk of bias (category D)[b]	High risk of bias (category E)[c]	High risk of bias (category G)[d]

(Continued)

Simmons 2012	ND

[a]Clear that outcome was measured and analysed; trial report states that outcome was analysed but reports only that result was not significant.
(Classification 'A', table 2, Kirkham 2010)
[b]Clear that outcome was measured and analysed; trial report states that outcome was analysed but reports no results.
(Classification 'D', table 2, Kirkham 2010)
[c]Clear that outcome was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported due to non-significant results.
(Classification 'E', table 2, Kirkham 2010)
[d]Unclear whether outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results.
(Classification 'G', table 2, Kirkham 2010)

ND: none detected.

Appendix 11. Definition of endpoint measurement (I)[a]

Study ID	All-cause mortality	Diabetes-related mortality	Diabetes-related morbidity	Incidence of type 2 diabetes	Health-related quality of life	Adverse events	Socioeconomic effects
Simmons 2012	The England and Wales Office of National Statistics provided death certificate copies of deceased participants. The General Register Office of Scotland and the Central Statistics Office of Ireland provided the vital status of participants who moved to these areas (IO).	Diabetes stated as cause of death on death certificates (IO).	Diabetes was included anywhere on the death certificate (IO).	NR	EQ-5D generic quality of life instrument comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status. The score ranges from −0.3 to 1, with the maximum score of 1 indicating the best health state (SO). Mental health: SF-8 mental health summary score, which assesses psychological distress and well-being. The score ranges from 0 to 100, with the maximum score of 100 indicating the best mental health state (SO).	—	NR

—: denotes not reported

[a]In addition to definition of endpoint measurement, description of who measured the outcome (**AO**: adjudicated outcome measurement; **IO**: investigator-assessed outcome measurement; **SO**: self-reported outcome measurement).

EQ-5D: EuroQol measure of health outcome; **NR**: not reported; **SF-8:** 8-item Short Form Health Survey.

Appendix 12. Adverse events (I)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Deaths (N)	Deaths (% of participants)	Participants with at least 1 adverse event (N)	Participants with at least 1 adverse event (%)	Participants with at least 1 severe/serious adverse event (N)	Participants with at least 1 severe/serious adverse event (%)
Simmons 2012	I: Individuals at high risk for diabetes invited for screening	16,047	1532	9.6	—	—	—	—
	C: Individuals at high risk for diabetes not invited for screening	4137	377	9.1	—	—	—	—

—: denotes not reported

C: comparator; **I**: intervention.

Appendix 13. Adverse events (II)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants discontinuing trial due to an adverse event (N)	Participants discontinuing trial due to an adverse event (%)	Participants with at least 1 hospitalisation (N)	Participants with at least 1 hospitalisation (%)	Participants with at least 1 outpatient treatment (N)	Participants with at least 1 outpatient treatment (%)
Simmons 2012	I: individuals at high risk for diabetes invited for screening	16,047	—	—	—	—	—	—
	C: individuals at high risk for diabetes not invited for screening	4137	—	—	—	—	—	—

—: denotes not reported

C: comparator; **I**: intervention.

Appendix 14. Survey of study investigators providing information on included studies

Included studies		Date study author contacted	Date study author replied	Date study author was asked for additional information (short summary)	Date study author provided data (short summary)
Simmons 2012		26 March 2020	No answer	NA	NA
Studies awaiting assessment	**Study completion date**	**Date study author contacted**	**Date study author replied**	**Date study author was asked for additional information (short summary)**	**Date study author provided data (short summary)**
Scherstén 1966	PM	Contact details for the author were unavailable; study was published over 50 years ago.	NA	NA	NA
Klijs 2012	RT (ISRCTN75983009)	February 2018; April 2020	No answer	NA	NA
Ongoing trials (with an estimated study completion date more than 1 year in the past)	**Study completion date**	**Date study author contacted**	**Date study author replied**	**Date study author was asked for additional information (short summary)**	**Date study author provided data (short summary)**
None	NA	NA	NA	NA	NA

NA: not applicable; **PM**: published manuscript; **RT**: registered trial.

Appendix 15. Checklist to aid consistency and reproducibility of GRADE assessments

		(1) All-cause mortality	(2) Diabetes-related mortality	(3) Diabetes-related morbidity	(4) Incidence of type 2 diabetes	(5) Health-related quality of life	(6) Adverse events	(7) Socioeconomic effects
Study ID limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	Subsample only	—	Subsample only (the response rate was 62% in the screening group and 53% in the control group)	—	—
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear					
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome was not likely to have been influenced by lack of blinding?	Yes	Yes					
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to have been influenced by lack of blinding?	Yes	Yes					
	Was an objective outcome used?	Yes	Yes					
	Were more than 80% of participants enrolled in the trials included in the analysis (i.e. no potential attrition bias)?[e]	Yes	Yes					
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes					
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes					
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes					
Inconsistency[b]	Point estimates did not vary widely?	NA	NA					
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least 1 of the included studies point es-	NA	NA					

(Continued)

	timate; some: confidence intervals overlap but not all overlap at least 1 point estimate; no: at least 1 outlier: where the confidence intervals of some of the studies do not overlap with those of most included studies)?		
	Was the direction of effect consistent?	NA	NA
	What was the magnitude of statistical heterogeneity (as measured by I^2): low (I^2 < 40%), moderate (I^2 40% to 60%), high (I^2 > 60%)?	NA	NA
	Was the test for heterogeneity statistically significant (P < 0.1)?	NA	NA
Indirectness	Were the populations in the included studies applicable to the decision context?	Applicable	Applicable
	Were the interventions in the included studies applicable to the decision context?	Applicable	Applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes
	Was the outcome time frame sufficient?	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	No (↓)	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[e]	NA	NA
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes	No (↓)

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes
	Was grey literature searched?	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes
	There was no industry influence on the studies included in the review?	Yes	Yes
	There was no evidence of funnel plot asymmetry?	NA	NA
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear

—: denotes not reported

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials.
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2.

[c]When judging the width of the confidence interval, it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of findings' table(s).

Appendix 16. Health-related quality of life: instruments

Instrument	Dimensions (subscales) (no. of items)	Validated instrument	Answer options	Scores	Minimum score Maximum score	Weighting of scores	Direction of scales	Minimal important difference
EQ-5D (G) (employed in Simmons 2012)[a]	Health utility	Yes	1 = no problem, 2 = moderate problem, 3 = severe problem	Scores for health utility	Minimum score: −0.3 Maximum score: 1	No	Higher values indicate best health state.	-
SF-8 (G) (employed in Simmons 2012)[a]	Mental health	Yes	5-to-6-point Likert scale	Scores for mental health	Minimum score: 0 Maximum score: 100	No	Higher values indicate best health state.	"50 points represents the national standard value for health and functioning"

[a]Subsample only: the response rate was 62% in the screening group and 53% in the control group.

EQ-5D: EuroQol measure of health outcome; **SF-8**: 8-item Short Form Health Survey; **G**: Generic: not reported.

WHAT'S NEW

Date	Event	Description
2 June 2020	Amended	Addition of the statement of Solange Durao to external sources.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 5, 2020

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

Nasheeta Peer (NP): design and write-up of updated protocol, acquisition of study reports, study selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Yusentha Balakrishna (YB): study selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Solange Durao (SD): design and write-up of updated protocol, protocol draft, acquisition of study reports, study selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

DECLARATIONS OF INTEREST

NP: none known.

YB: none known.

SD: none known.

SOURCES OF SUPPORT

Internal sources

- South African Medical Research Council, South Africa

External sources

- NP was supported by a fellowship offered by Cochrane South Africa, South African Medical Research Council, funded by the Effective Health Care Research Consortium. This Consortium is funded by UK aid from the UK Government for the benefit of developing countries. The views expressed in this publication do not necessarily reflect UK government policy., South Africa

  Grant Number 5242
- SD was partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It is funded by UK aid from the UK Government. The views expressed in this publication do not necessarily reflect UK Governments official policies., South Africa

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The ADDITION-Cambridge study also reported on cardiovascular and cancer mortality. Although these outcomes were not prespecified in our protocol, we have reported on both outcomes in the review.

NOTES

Portions of the Background and Methods sections, the Appendices, Additional tables, and Figures 1 to 3 of this review are based on a standard template established by Cochrane Metabolic and Endocrine Disorders.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Diabetes Mellitus, Type 2 [*diagnosis] [mortality]

MeSH check words

Female; Humans; Male; Middle Aged